THE PROPHYLAXIS OF IRON-DEFICIENCY ANÆMIA IN PREGNANCY

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IN the hundred and twenty years since Nasse wrote his original monograph on anæmia in pregnancy, a voluminous literature has appeared. Some of the century-old controversies about the cause of this anæmia have been resolved with the advent of methods for measuring directly the plasma volume and red-cell mass. It is now agreed that there are three main factors:

(1) An increase in plasma volume that outstrips the simultaneous increase in red-cell mass (Dieckmann and Wegner 1934, Thomson et al. 1938, Roscoe and Donaldson 1946, McLennan and Thouin 1948, Tysoe and Lowenstein 1950, Lund 1951, Berlin et al. 1953).

(2) A deficiency of iron due to the demands of the fœtus (Rath et al. 1950, Moore 1955, *Lancet* 1955).

(3) A deficiency of folic acid and possibly of cyanocobalamin due to the increased demands of the fœtus and of the pregnant woman and to impaired absorption during pregnancy.

The megaloblastic anæmia of pregnancy accounts for only a very small proportion of cases of anæmia during pregnancy.

The anæmias of pregnancy not due to folic-acid or cyanocobalamin deficiency have been divided by many authors into two groups—"hypochromic" and the so-called "physiological", the former being indistinguishable from iron-deficiency anæmia in non-pregnant women. The "physiological" anæmia differs in certain important respects from iron-deficiency anæmia in non-pregnant women, as shown in table I, which was constructed after studying the published work of Dieckmann and Wegner (1934), Goodall and Gottlieb (1936), Fay et al. (1949), Rath et al. (1950), Hahn et al. (1951), Caton et al. (1951), Berlin et al. (1953), and Verel et al. (1956). Because of these dissimilarities, it has been argued that the "physiological" anæmia cannot be due to iron deficiency. This view has been supported on the grounds that the red-cell mass often increases during pregnancy and returns to normal in the puerperium (Caton et al. 1949, 1951, Berlin et al. 1953). The argument, however, that has swayed medical opinion most cogently against the idea of a "physiological" anæmia of pregnancy has been the fact that it can usually be corrected with iron (Scott and Govan 1949, Klopper and Ventura 1951, Benstead and Theobald 1952, Davis and Jennison 1954, Lillie et al. 1954, Fisher and Biggs 1955, Edgar and Rice 1956), which often causes a rise in mean corpuscular hæmoglobin concentration (M.C.H.C.) even when the latter was in the normal range before treatment. The view that an anæmia which responds to iron in the same manner as a mild iron-deficiency anæmia cannot be physiological has recently gained wide acceptance, and many authorities now recommend that all women should receive iron supplements during pregnancy (*Lancet* 1955, 1956).

At the same time it should be noted that some workers (Fisher and Biggs 1955, Edgar and Rice 1956) have found that 10–20% of patients are anæmic in late pregnancy even when adequate doses of iron have been prescribed. Several possible explanations have been suggested: (1) failure to take the prescribed iron, (2) failure to absorb iron, (3) mild folic-acid deficiency, (4) an unusually large increase in plasma volume. Since the last is probably the most important factor, a simple, safe and satisfactory procedure for the measurement of red-cell mass which did not involve the use of radioactive isotopes would be very helpful in determining the nature of these refractory cases.

The incidence of anæmia varies considerably in different populations, according to the economic conditions (Strauss and Castle 1932, Davidson et al. 1935, Fullerton 1936, Doyle and McGrath 1954), and considerable social changes have taken place in Edinburgh since the last survey (Roscoe and Donaldson 1946). To help formulate a practical policy for the prophylaxis of iron-deficiency anæmia in pregnancy we have therefore undertaken a study on patients attending the Simpson Memorial Maternity Pavilion, Edinburgh, to ascertain:

(1) The incidence of anæmia in pregnancy.

(2) The effect of season, age, parity, recent pregnancy, and duration of pregnancy on the incidence and degree of anæmia.

(3) The adequacy of the present diet of Edinburgh mothers.

(4) The most suitable forms of oral iron to administer, if supplements are necessary, in regard to their efficiency, economy, and lack of undesirable side-effects.

(5) The stage in pregnancy at which iron supplements should be started.

(6) Whether the addition of ascorbic acid to ferrous gluconate pills confers any advantage upon them.

The effect of adding ascorbic acid to the iron pills was investigated because: (*a*) ascorbic acid aids the absorption of iron (Powell 1944, Moore 1955); (*b*) a deficiency of ascorbic acid increases the incidence of anæmia in pregnancy, and the administration of ascorbic acid corrects the anæmia, though less effectively than iron (Scott and Govan 1949); and (*c*) tablets containing ascorbic acid as well as iron are stated to be better tolerated than iron alone (Fisher and Biggs 1955).

Investigation of Incidence of Anæmia

To obtain information in regard to problems 1 and 2 a study was made of the case-notes of all the patients attending the antenatal clinic of the Simpson Memorial Maternity Pavilion, in the periods February–March and August–September of 1955 and 1956. After excluding patients who were found to have any disease likely to

TABLE I—COMPARISON OF IRON-DEFICIENCY ANÆMIA WITH "PHYSIOLOGICAL" ANÆMIA OF PREGNANCY

—	Iron-deficiency anæmia	"Physiological" anæmia of pregnancy
Colour index	Low	Normal
M.C.H.C.	Low	Low normal
M.C.V.	Low	High normal
Reticulocyte count	Low	Raised
Serum iron	Low	Normal or low
Iron-binding capacity (I.B.C.)	High	High
Ratio of serum iron to I.B.C.	Very low	Low
Iron absorption	Increased	Increased
Free erythrocyte protoporphyrin	Increased	Slightly increased
Serum copper	High	High
Total red cell mass	Low	Normal or increased
Total body hæmoglobin	Low	Normal or increased
Plasma volume	Increased +	Increased +++
Response to iron therapy	Rise in Hb +++	Rise in Hb +

cause anæmia or who were receiving iron at the time of their first visit, the number of case-notes available for analysis was 1994—an average of about 500 patients for each of the four periods. Hæmoglobin levels were estimated routinely at the first visit by the oxyhæmoglobin method, in an E.E.L. photoelectric colorimeter, using capillary blood obtained by pricking the finger.

Of these 1994 patients, 1071 attended the clinic for the first time before the twelfth week of pregnancy (table II). Of this number 631 required and received iron medication; the remaining 440 patients were given no iron. Table VII summarises the changes in hæmoglobin level in these 440 women between the first visit and the 23rd to 27th week of pregnancy.

Tables II–VI show the incidence of anæmia in the 1994 patients in relation to the stage of pregnancy at their first visit, the season when they were first seen at the clinic, their age, their parity, and the number of their pregnancies within the previous five years.

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Incidence of anæmia (table II).—The mean hæmoglobin level of 1071 women seen initially in the first 11 weeks of pregnancy, a period during which the occurrence of hydræmia is insignificant, was 12·9 g. per 100 ml. (88%). (Hæmoglobin percentages given are based on the scale that 14·8 g. per 100 ml. = 100%.) A hæmoglobin level below 10·4 g. (70%) was found in 2% of the women, while 32% had a level below 12·6 g. (85%).

TABLE II—HÆMOGLOBIN LEVEL AT FIRST ANTENATAL VISIT IN 1955–56

Week in pregnancy when Hb level was estimated	No. of patients	Mean hæmoglobin level		Standard deviation	
		g. per 100 ml.	%	g. per 100 ml.	%
1–40	1994	12·6	85	1·30	8·8
1–11	1071	13·0	88	1·39	9·4
12–23	698	12·4	84	1·31	8·9
24–40	225	11·6	78	1·32	8·9

The mean hæmoglobin level was lower in women first seen at a later stage in pregnancy, the difference being highly significant ($P < 0.001$). Of the 225 women first seen at the 24th week or later, 13·7% had a hæmoglobin level of less than 10·4 g. per 100 ml. (70%) and 78·1% had a hæmoglobin level of less than 12·6 g. per 100 ml. (85%).

Seasonal variation (table III).—Women first seen at the end of the winter (i.e., in February and March) had higher hæmoglobin levels on the average than those first seen at the end of the summer (i.e., in August and September). The difference between these two groups is highly significant ($P < 0.001$).

Effect of age (table IV).—To assess the effect of age on the incidence of anæmia, without the complicating factors of previous pregnancies and iron therapy, the case-records of 300 primigravidæ seen in 1955 who were not receiving iron therapy at the time of examination were analysed. No significant difference was found between the mean initial hæmoglobin levels of women under and over 25 years of age. Subdivision into narrower age-groups again showed no significant difference. Age has therefore been ignored in assessing the effect of parity.

Effect of parity (table V).—The mean hæmoglobin levels of 618 primigravidæ and 390 parous women were compared at different stages of pregnancy. No significant difference was found ($P > 0.3$).

TABLE III—SEASONAL VARIATION IN THE INCIDENCE OF ANÆMIA IN PREGNANCY. COMPARISON BETWEEN WOMEN WHO FIRST ATTENDED THE ANTENATAL CLINIC AT THE END OF THE SUMMER (AUGUST–SEPTEMBER) AND AT THE END OF WINTER (FEBRUARY–MARCH) 1955 AND 1956

Stage in pregnancy when Hb level was estimated (weeks)	Season	No. of patients	Mean hæmoglobin level		Standard deviation	
			g. per 100 ml.	%	g. per 100 ml.	%
0–11 ..	Summer	534	12·5	84	1·11	7·5
	Winter	537	13·5	91	1·26	8·5
12–23 ..	Summer	358	12·0	81	1·11	7·5
	Winter	340	12·8	87	1·36	9·2
24–40 ..	Summer	99	11·1	75	1·23	8·3
	Winter	126	11·8	80	1·30	8·8

Effect of recent pregnancies (table VI).—The mean hæmoglobin levels of women who had borne no children, one child, or two or more children within the five-year period preceding the present pregnancy were compared. There was no significant difference between the groups.

Fall in hæmoglobin level during second trimester.—The mean fall in hæmoglobin level between the first estimation (during first 11 weeks of pregnancy) and second estimation (23rd–27th week of pregnancy) in the 440 women who were known to have received no iron is shown in table VII, where it is compared with the initial hæmoglobin level. The fall was greatest in those women with an initially high hæmoglobin level, even when it was expressed as a percentage of the original level. The difference in the mean fall in hæmoglobin level of patients with an initial hæmoglobin level of 12·6 g. per 100 ml. (85%) or more was significantly greater ($P < 0.01$) than in those patients with an initial hæmoglobin level below 12·6 g.

Investigation of Iron Preparations

To obtain information about the potency and toxicity of certain iron preparations an investigation was undertaken of all women attending the antenatal clinic of the Simpson Memorial Maternity Pavilion between March, 1956, and June, 1957, during their 24th or 25th week of pregnancy, provided that:

(1) Their hæmoglobin level was 10·4 g. per 100 ml. or above.

(2) They had no disease likely to cause anæmia or excessive hydræmia.

(3) They did not have twins.

(4) They were not already receiving iron therapy.

(5) They intended to continue attending the antenatal clinic till term.

The 430 women accepted for this investigation were assigned by random selection (choosing a card from a pack) to one of four groups. Group A (20%) received ferrous sulphate; group B (20%) received ferrous gluconate; group C (20%) received ferrous gluconate plus ascorbic acid; and group D (40%) formed the control group which received pills containing lactose.

The pills prescribed were identical in shape, colour, and

TABLE IV—EFFECT OF AGE ON THE LEVEL OF HÆMOGLOBIN OF 300 PRIMIGRAVIDÆ

Stage in pregnancy when Hb level was estimated (weeks)	Age	No.	Mean hæmoglobin level		Standard deviation	
			g. per 100 ml.	%	g. per 100 ml.	%
0–11	Under 25	97	12·9	87	0·83	5·6
	25 and over	90	12·9	87	1·03	7·0
12–23	Under 25	81	12·2	83	0·99	6·7
	25 and over	32	12·0	81	1·04	7·0

TABLE V—EFFECT OF PARITY ON THE HÆMOGLOBIN LEVEL OF 618 PRIMIGRAVIDÆ AND 390 PAROUS WOMEN

Stage in pregnancy when Hb level was estimated (weeks)	Season	No. of patients	Mean hæmoglobin level		Standard deviation	
			g. per 100 ml.	%	g. per 100 ml.	%
1–11 Prim. ..	Summer	184	12·3	83	1·02	6·9
Parous. ..	Summer	81	12·3	83	1·05	7·1
Prim. ..	Winter	181	13·0	88	1·20	8·1
Parous. ..	Winter	94	13·2	89	1·11	7·5
12–23 Prim. ..	Summer	97	11·8	80	1·12	7·6
Parous. ..	Summer	71	11·9	81	1·07	7·2
Prim. ..	Winter	103	12·4	84	1·26	8·5
Parous. ..	Winter	65	12·4	84	1·38	9·3
24–40 Prim. ..	Summer	21	11·2	76	1·27	8·6
Parous ..	Summer	33	11·1	75	1·05	7·1
Prim. ..	Winter	32	11·5	78	1·26	8·5
Parous. ..	Winter	36	11·6	78	1·01	6·8

costing. As the control group was larger than the others, it was necessary for the doctors conducting the trial to know which were the control pills; the other three preparations were known as pills A, B, and C, and their identity was not known to patients or doctors until the trial was finished and the results had been analysed.

Careful consideration was given to the dosage of iron to be incorporated in the pills. It was essential that the daily iron intake should be the same irrespective of which preparation was being taken. The dose of ferrous gluconate usually recommended is one 300 mg. (gr. 5) pill containing 35 mg. of elemental iron, given three times a day, making a total of 105 mg. of iron daily. Ferrous sulphate, however, is usually prescribed as one 180 mg. (gr. 3) pill containing 60 mg. of elemental iron, three times a day, making a total of 180 mg. of iron daily. We had to decide at the outset whether to increase the dose of elemental iron in each ferrous-gluconate pill to 60 mg.—i.e., approximately double the usual therapeutic dose—or to reduce the amount of elemental iron in each ferrous-sulphate tablet from 60 mg. to 35 mg. The latter choice was made because we wished to know not only about the therapeutic efficiency of ferrous gluconate and the incidence of side-effects when it was given in the usual dosage mentioned above, but also whether the addition of 25 mg. of ascorbic acid to each ferrous-gluconate pill would increase its efficiency or reduce its toxicity. Accordingly each ferrous-sulphate and ferrous-gluconate pill used in this investigation contained 35 mg. of elemental iron.

Each patient was given both oral and written instructions which explained that she was going to be given a preparation of iron to prevent or cure the anæmia which tended to develop in pregnancy. It was also emphasised that the pills were to be taken three times a day after food, and stress was placed on the need to take them regularly for the period prescribed. No mention was made of control pills containing lactose. The possibility that 40% of pills ingested did not contain iron was apparently not suspected by the patients, since only 2 commented on the fact that their motions were not black.

Patients were recalled for the second interview at the 37th week, when each was asked to estimate her weekly intake of certain iron-containing foods (meat, liver, bacon, fish, eggs, soups, potatoes, cereals, bread, milk, beverages, chocolate) during the period of the trial. From this her daily intake of iron was calculated; figures for the iron content of foods were taken from tables constructed by McCance and Widdowson (1946).

At this second interview patients were asked whether they had suffered any symptoms from taking the pills, and if so whether they interfered with the treatment. Symptoms were graded "mild" (no interference with treatment) "moderate" (temporary interruption of treatment) and "severe" (obliged to stop treatment). Only gastrointestinal symptoms were recorded as being due to the pills. Patients were also asked whether they had taken the pills conscientiously. Only 6 of the patients who did not complain of intolerance to iron admitted that they had taken the pills irregularly.

37 women were unable to take the prescribed course of pills because of "severe" toxic effects. In addition 61 failed to complete the trial because of premature delivery, conditions complicating pregnancy (e.g., toxæmia), intercurrent illness, removal from the district, or unwillingness to cooperate.

Hence of the original 430 patients, 332 took their pills regularly and came to the second interview. A study has been made of the potency of the different oral iron preparations used in the treatment of this group of women. The 61 women who failed to attend were sent a questionnaire in which they were asked to record any gastrointestinal symptoms experienced while taking the pills. From these questionnaires and from the information given by the 369 women (332 + 37) attending the second interview, it was possible to analyse the incidence of toxic symptoms in a total of 410 patients.

TABLE VI—EFFECT ON HÆMOGLOBIN LEVEL OF NUMBER OF PREGNANCIES WITHIN THE LAST FIVE YEARS (PATIENTS SEEN IN 1955)

Stage in pregnancy when Hb level was first estimated (weeks)	Season	Pregnancies within last five years	No. in group	Mean hæmoglobin level		Standard deviation	
				g. per 100 ml.	%	g. per 100 ml.	%
0–11	Summer	0	202	12·8	87	1·08	7·3
		1	56	12·4	84	1·29	8·7
		2 or more	11	12·1	82	1·15	7·8
	Winter	0	173	13·8	93	1·21	8·2
		1	75	14·1	96	1·29	8·7
		2 or more	15	14·4	97	1·45	9·8
12–23	Summer	0	120	12·1	82	1·10	7·4
		1	48	12·2	82	1·18	8·0
		2 or more	23	12·0	81	1·11	7·5
	Winter	0	106	13·2	89	1·29	8·7
		1	42	13·3	90	1·55	10·5
		2 or more	24	12·8	87	1·27	8·6

Venous blood was taken, with minimum stasis, at the 24–25th week and at the 37th week, and the hæmoglobin level (Hb), red-cell count (R.B.C.), and packed-cell volume (P.C.V.) measured.

Hæmoglobin was estimated by the alkaline hæmatin method, using an E.E.L. photoelectric colorimeter; red-cell counts were performed in duplicate in Neubauer counting-chambers; packed-cell volumes were measured after centrifugation for thirty minutes at 3000 r.p.m. in a standard hæmatocrit centrifuge. Between the two blood-tests the patients were not

TABLE VII—FALL IN HÆMOGLOBIN LEVEL DURING SECOND TRIMESTER IN 440 PATIENTS NOT RECEIVING IRON THERAPY

Initial hæmoglobin range		No. of patients	Mean fall in hæmoglobin level		Standard deviation		Mean fall in hæmoglobin level as % of initial hæmoglobin level
g. per 100 ml.	%		g. per 100 ml.	%	g. per 100 ml.	%	
10·4–10·9	70–74	5	0·7	5	0·36	2·4	6·4
11·1–11·7	75–79	25	1·2	8	0·70	4·7	10·3
11·8–12·4	80–84	79	1·5	10	0·77	5·2	12·7
12·6–13·2	85–89	133	1·7	12	0·76	5·1	12·9
13·3–13·9	90–94	102	2·1	14	0·80	5·4	15·5
14·1–14·6	95–99	66	2·5	17	0·84	5·7	17·2
14·8–15·4	100–104	30	3·0	20	1·60	10·8	19·6

TABLE VIII—CHANGE IN HÆMOGLOBIN LEVEL, RED-CELL COUNT, AND PACKED-CELL VOLUME BETWEEN 24–25TH AND 37TH WEEK OF PREGNANCY IN THE FOUR TREATMENT GROUPS

Hæmoglobin Levels

Treatment	No. in group	Initial mean Hb level		Mean change in Hb level		Standard deviation	
		g. per 100 ml.	%	g. per 100 ml.	%	g. per 100 ml.	%
Ferrous sulphate	67	12·0	81	+0·7	+5	1·12	7·6
" gluconate	67	12·0	81	+1·1	+7	1·18	8·0
" " plus ascorbic acid	70	11·9	80	+1·0	+7	0·90	6·1
" " (total)	137	12·0	81	+1·1	+7	1·06	7·2
Control	128	12·1	82	−0·4	−3	1·15	7·8

Red-cell Count

Treatment	No. in group	Initial mean R.B.C. (million per c.mm.)	Mean change in R.B.C. (million per c.mm.)	Standard deviation (million per c.mm.)
Ferrous sulphate	67	3·9	+0·3	0·30
" gluconate	67	3·9	+0·4	0·40
" " plus ascorbic acid	70	3·9	+0·4	0·35
" " (total)	137	3·9	+0·4	0·37
Control	128	3·9	+0·0	0·36

Packed-cell Volume

Treatment	No. in group	Initial mean P.C.V. (%)	Mean change in P.C.V. (%)	Standard deviation (%)
Ferrous sulphate	67	36·4	+2·7	2·3
" gluconate	67	36·1	+3·2	2·7
" " plus ascorbic acid	70	36·0	+2·7	2·3
" " (total)	137	36·0	+2·9	2·2
Control	128	36·3	−0·6	1·9

normally seen by the investigators, but were supervised by the obstetricians. This supervision included further routine hæmoglobin estimations—usually two. Any patient whose hæmoglobin fell below 10·4 g. per 100 ml. (70%) was referred to the investigators. 11 patients taking control tablets were seen on this account; they were excluded from the trial and given iron pills. All responded normally. 4 who were taking iron pills were referred for the same reason. Additional counts were carried out: 1 patient was found to have megaloblastic anæmia of pregnancy; the remaining 3 were left on the same treatment, and eventually responded with a rise in hæmoglobin level.

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Dietary survey.—The replies by 95 successive patients taking control pills, who answered a more detailed dietary questionnaire, were analysed. The mean dietary intake of iron was estimated at about 11 mg. This was not the total intake, for only the major iron-containing foods were included in the questionnaire, but it was thought to represent 80–90% of the intake for the average woman. This gave an estimated mean iron consumption of approximately 13 mg. daily—an intake slightly below the minimum level of 15 mg. recommended for pregnant women by the B.M.A. Sub-Committee on Nutrition in 1950.

Effect of diet on hæmoglobin level.—The fall in hæmoglobin level in the 95 women in the control group during the last trimester of pregnancy has been compared with their estimated dietary intake of iron. The mean fall in 26 patients whose diet was unsatisfactory as regards iron (i.e., reckoned to contain less than 10 mg. daily) was 0·6 g. per 100 ml. (4%), whereas the mean fall in 69 patients whose dietary intake of iron was reckoned to be more than 10 mg. (16 of whom ingested more than 14 mg. daily) was 0·4 g. per 100 ml. (2·7%). It is obvious therefore that factors other than the total content of iron in the diet were important in determining the final hæmoglobin level. It is of interest that some women reckoned to be taking more than the recommended intake of 15 mg. of iron a day were found to have a considerable fall in hæmoglobin level.

Comparison of the iron preparations.—The changes in hæmoglobin level, red-cell count, and packed-cell volume in the four treatment groups are shown in table VIII. Hæmoglobin levels and packed-cell volume rose in each of the iron-treated groups and fell in the control group, the difference being significant ($P < 0.01$). The red-cell count rose slightly in the control group, but the rise in each treatment group was significantly greater ($P < 0.05$). These differences between the control and treatment groups would have been larger had not 11 patients who were originally assigned to the control group been excluded from the trial because their hæmoglobin level fell below 10·4 g. per 100 ml. (70%).

No significant difference between the changes in hæmoglobin level, red-cell count, and packed-cell volume was observed in the two groups treated with ferrous gluconate, with and without ascorbic acid ($P > 0.3$). We conclude, therefore, that the addition of ascorbic acid does not affect the therapeutic value of ferrous gluconate, either beneficially or adversely. Accordingly the two groups treated with ferrous gluconate have been amalgamated and compared with the group treated with ferrous sulphate. The rise in hæmoglobin level, red-cell count, and packed-cell volume in the ferrous-sulphate group is less than in the groups receiving ferrous gluconate; the difference is significant ($0.01 < P < 0.05$) for the red-cell count, barely significant ($P = 0.05$) for the hæmoglobin level, and not significant ($P < 0.05$) for the packed-cell volume.

The incidence of gastrointestinal intolerance to the pills is shown in table IX. There is no significant difference

TABLE IX—INCIDENCE OF GASTROINTESTINAL INTOLERANCE TO ORAL IRON PREPARATIONS

Iron preparation	No. in group	Percentage showing symptoms			
		Nil	Mild	Moderate	Severe
Ferrous sulphate	81	75	11	7	6
" gluconate	88	66	16	8	10
" " plus vitamin C	82	72	10	6	12
Control (lactose)	159	74	13	4	9

TABLE X.—FALL IN HÆMOGLOBIN LEVEL AND PACKED CELL VOLUME DURING THIRD TRIMESTER IN PATIENTS NOT RECEIVING IRON THERAPY

Initial Hb level		No. of patients	Hb level				P.C.V.	
			Mean change		Standard deviation		Mean change (%)	Standard deviation (%)
g. per 100 ml.	%		g. per 100 ml.	%	g. per 100 ml.	%		
10·36–11·69 ..	70–79	43	+0·10	+0·7	0·95	6·4	−0·2	3·9
11·84 and over ..	80	85	−0·62	−4·2	1·15	7·8	−0·8	3·3

between the control pills and the iron pills, or between the three iron preparations. This suggests that most of the symptoms attributed by the patients to iron medication were either incidental or psychogenic in origin. It was thought possible that the gastrointestinal symptoms (morning sickness, heartburn, constipation) which are liable to occur in pregnancy might be obscuring the incidence of symptoms due to iron intolerance. An investigation of the side-effects of oral iron medication was therefore carried out on 93 normal women who were not pregnant. The results (Kerr and Davidson 1958) are very similar to those in the pregnant women and clearly demonstrate the great importance of the psychological factor.

Discussion

Although severe anæmia is now uncommon in pregnant women in Edinburgh, the incidence of mild anæmia at the beginning of pregnancy is still sufficient to justify wide-scale prophylaxis with oral iron therapy. Like many other authors, we noted a fall in the hæmoglobin level in the later stages of pregnancy.

The seasonal variation in the incidence is interesting. Our findings that the incidence is highest at the end of summer contrasts with the finding of some other workers (Scott and Govan 1949, Lund and Kimble 1943, Doyle and McGrath 1954, Gatenby and Lillie 1955) who described a lower incidence in summer. We must frankly admit that we know of no satisfactory explanation of the seasonal fluctuations in the hæmoglobin level. They might reflect changes in the diet, but in our survey these were so small that they could have had no effect on the amount of iron in the food. Although no information was collected regarding the intake of fruit and vegetables, there are several reasons which convince us that the seasonal changes in the incidence of anæmia shown in table III are unlikely to be due to seasonal variations in the intake of iron and ascorbic acid derived from these sources.

No increase in susceptibility to anæmia was found with increasing age; this contrasts with the finding of Roscoe and Donaldson (1946); but these workers compared all women regardless of parity, whereas we compared primigravidæ only. Anæmia did not increase significantly with the number of children, or with the number of pregnancies in the previous five years. This is in marked contrast to the experience of one of us (S. D.) twenty-five years ago in Aberdeen. The most likely causes of the change are: (1) the great improvement in the social and economic status of the working classes, particularly in the past fifteen years; (2) the stress laid by teachers of medicine on the importance of menstruation and pregnancy in the ætiology of iron-deficiency anæmia; and (3) routine hæmoglobin estimations in antenatal clinics and maternity hospitals and the administration of iron to all patients who are found to need it.

The fall in hæmoglobin level during the second and third trimesters, noted by previous workers, was found in women who were not given iron. It is of interest that the women with initially high hæmoglobin levels sustained the biggest fall in hæmoglobin during the second trimester, and this was true also, though in lesser degree, during the third trimester (table X). The explanation is uncertain: possibly iron is absorbed more avidly in early pregnancy by patients who are already anæmic. Whatever the cause, the observation is of some practical importance because it means that a normal hæmoglobin level at the beginning of pregnancy, or even at the 24th week, does not guarantee the patient against anæmia at term. From the data used in compiling tables VII and X we were able to calculate that a woman (in the population studied) with an initial hæmoglobin range of 12·5 to 15·0 g. per 100 ml. (84–101%) at the beginning of pregnancy stands roughly a 10% chance of reaching "term" with a hæmoglobin level of less than 10 g. per 100 ml. (68%) if she is given no iron during pregnancy.

Administration of 105 mg. of iron daily between the 24th and 37th weeks caused a mean rise in hæmoglobin level, red-cell count, and packed-cell volume. This is a relatively small dose of iron and the final mean hæmoglobin level achieved—13·0 g. per 100 ml. (88%)—is not as high as that recorded by some other workers who used larger doses of iron, or the same dose for longer periods (Benstead and Theobald 1952, Edgar and Rice 1956). However, it is to be expected that the hæmoglobin level will rise further between the 37th week and term, as it rises slightly at this stage in pregnancy even in untreated patients; we feel that a final mean hæmoglobin level of about 13·5 g. (91%) at term is reasonably satisfactory. There are several reasons for giving iron routinely in late rather than early pregnancy. Firstly it has been shown that iron is better absorbed at this stage (Hahn et al. 1951). Secondly there is a considerable saving of money and trouble to the patient by limiting iron therapy to the last trimester. Thirdly the fœtal demands for iron are at their maximum. And fourthly therapeutic results will generally be found to be satisfactory.

Like Fisher and Biggs (1955) and Edgar and Rice (1956), we found that a proportion of the patients treated with iron failed to show a rise in hæmoglobin level (24% of those on ferrous sulphate and 23% of those on ferrous gluconate).

As a result of our investigations we suggest the following scheme of supervision for antenatal patients:

(1) Routine hæmoglobin estimation at the first antenatal visit. This has been the practice for many years in the Simpson Memorial Maternity Pavilion.

(2) Iron therapy from the first visit for all patients with an initial hæmoglobin level of less than 12·6 g. per 100 ml. (85%).

(3) Routine administration of elemental iron in a dosage of at least 105 mg. daily to all patients from the 24th week to term. This dosage is provided by one 300 mg. (gr. 5) pill of ferrous gluconate, three times a day. The customary dose of ferrous sulphate is one 180 mg. (gr. 3) pill three times a day which provides a much greater amount of elemental iron, namely 180 mg. per day.

The choice of preparation for iron therapy remains

controversial. This study suggests that ferrous gluconate may be slightly more efficient than ferrous sulphate (when given in the same dosage in terms of elemental iron—namely, 105 mg. daily) in raising the hæmoglobin level, but the difference is barely significant. Lillie et al. (1954) claim that ferrous gluconate is slightly superior to ferrous sulphate in restoring the hæmoglobin level of anæmic persons, even when the amount of iron in the dose of ferrous sulphate given was greater. However, the level of significance is not stated and their two groups of patients were not selected at random or concurrently. In contrast O'Sullivan et al. (1955) in a very carefully controlled investigation into the treatment of iron-deficiency anæmia in non-pregnant patients could find no significant difference in therapeutic efficacy between ferrous gluconate, ferrous succinate, and ferrous sulphate, all three preparations being given in a daily dose of 210 mg. of elemental iron. It seems to us, therefore, only reasonable to believe that better results would be obtained from giving 180 mg. of iron daily in the form of ferrous sulphate than from giving ferrous gluconate in a daily dose containing 105 mg. of iron; in which case the choice of preparation will depend essentially on relative cost and the frequency and severity of undesirable side-effects.

From our inquiries in Edinburgh we are satisfied that ferrous sulphate is the least expensive preparation of iron available (Davidson and Richmond 1958).

As already noted, we have not been able to demonstrate any difference in the incidence of gastrointestinal intolerance between women receiving ferrous sulphate and those receiving ferrous gluconate—105 mg. of iron daily in each case. In fact, the incidence was the same in those taking the control lactose pills. We attach great importance to the psychological factor in iron intolerance, and our experience is that the great majority of persons, pregnant or non-pregnant, can take one gr. 3 ferrous-sulphate tablet thrice daily without experiencing any significant side-effects, provided the tablet is always taken after meals and the patient is assured by her doctor that the pills will cause no discomfort.

We have not demonstrated that the addition of ascorbic acid to ferrous gluconate increases its therapeutic efficiency or reduces its side-effects. This conclusion does not necessarily apply to populations whose diet contains less ascorbic acid, but in Britain today the use of iron-plus-ascorbic-acid pills appears to be a needless expense.

Summary

(1) The incidence of anæmia in pregnancy in Edinburgh in 1955 and 1956 has been estimated. Although severe anæmia is rare at the beginning of pregnancy, mild anæmia (Hb < 12·6 g. per 100 ml. [85%]) is common.

(2) No correlation has been found between the incidence of anæmia and age, parity, or the number of pregnancies within the previous five years. Possible reasons for these findings are discussed.

(3) An estimate of the average daily dietary intake of iron in pregnant women in Edinburgh suggests that it is slightly less than the 15 mg. usually recommended. The incidence or degree of anæmia was not found to correspond closely with the dietary intake of iron.

(4) Oral administration of iron supplements during the third trimester corrects the anæmia of pregnancy in about 80% of cases, even when the initial mean corpuscular hæmoglobin content is normal. This time of administration appears to be suitable for routine purposes.

(5) As regards gastrointestinal side-effects, no difference was found between ferrous sulphate and ferrous gluconate, given in doses containing 105 mg. of iron daily. Neither preparation caused significantly more unpleasant gastrointestinal symptoms than the other or than the control pills containing lactose.

(6) The addition of ascorbic acid to ferrous-gluconate pills has not been shown to increase their therapeutic efficacy or to reduce their toxic effects.

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" The need for accuracy, orderliness and a strict observance of rules increases in proportion as clinical and surgical techniques become more complex, more scientific, more a matter of the co-ordinated and carefully timed activity of a medical and nursing team. Moreover, many of the new therapeutic and diagnostic procedures are, not infrequently, a serious threat to the patient's life. As the risk increases so does the need for accuracy and order. Thus, the system of rules and regulations which governs the performance of duties and the hierarchical relationships between different medical and nursing groups tends to become more complex and rigid."—RICHARD M. TITMUSS, *Essays on " The Welfare State "*, p. 201. London, 1958.

GASTROINTESTINAL INTOLERANCE TO ORAL IRON PREPARATIONS

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IT was the opinion of Thomas Sydenham that "iron may be given in the largest doses without inconvenience". His optimistic view has been shared in later generations by the originators of a large number of oral iron preparations which now compete for favour in the advertisement columns of the medical press. There is, however, a widespread belief among patients that iron inevitably causes gastrointestinal disturbance, particularly constipation.

To most patients ten years ago "iron" was synonymous with green ferrous-sulphate tablets. This preparation's popularity with the medical profession was well deserved. In correcting iron-deficiency anæmia it had been found at least as effective as any of the other available preparations (ferrous chloride, ferrous carbonate, iron and ammonium citrate, colloidal iron) and it had a considerable advantage in cost and convenience (Davidson and Fullerton 1938). During the past ten years a number of organic iron preparations have appeared on the market, and have been widely used. It is therefore desirable to re-examine the question of which oral preparation of iron is the most suitable for the treatment of anæmia, in both pregnant and non-pregnant patients.

O'Sullivan et al. (1955) compared three of the most popular preparations—ferrous sulphate, ferrous gluconate, and ferrous succinate. They gave the three compounds, in doses containing equal amounts of elemental iron (210 mg. daily) to matched groups of patients, and found similar rises in hæmoglobin level. Few other comparisons between iron compounds have been made with the same control of dosage and type of patient, but numerous papers attest the therapeutic effectiveness of most of the popular iron pills. Ferrous sulphate (Benstead and Theobald 1952, Devoe and Moses 1954, Talaga 1955, Gatenby and Lillie 1955, O'Sullivan et al. 1955), ferrous gluconate (Jasinski 1949, Haler 1952, Gatenby and Lillie 1955, O'Sullivan et al. 1955), ferrous succinate (O'Sullivan et al. 1955, Gillhespy 1955, Cope et al. 1956, Storm Mathiesen and Petersen 1956), ferrous calcium citrate (Talaga 1955), and several other compounds (Davidson and Fullerton 1938) have been shown to be capable of correcting iron-deficiency anæmia. In most of the papers cited, a rise in hæmoglobin level of more than 1% per day was obtained when the pills were taken conscientiously in the recommended dosage. Since the published evidence does not show that any one of these compounds is more efficient than the others, the choice between them depends mainly on two factors—cost and incidence of side-effects.

With regard to cost we are satisfied that ferrous sulphate is the least expensive preparation of iron available. (Davidson and Richmond 1958.) With regard to side-effects, experiments on animals have shown that in *very large* doses ferrous sulphate is appreciably more toxic than comparable amounts of iron and ammonium citrate, and two to five times as toxic as ferrous gluconate (Hoppe et al 1955, Brown and Gray 1955). Accidental poisoning with ferrous sulphate, usually in children, has sometimes been fatal (Reissman et al. 1955). It does not appear, however, that the symptoms of which patients complain when taking therapeutic doses of iron are simply milder forms of those caused by acute poisoning, since the latter are partly due to excessive absorption of iron (Reissman and Coleman 1955). For instance, constipation is the most common complaint of patients taking iron, whereas diarrhœa is an almost constant feature of ferrous-sulphate poisoning.

Published reports of the incidence and severity of gastrointestinal intolerance to therapeutic doses of iron vary greatly.

This variation is seen particularly with ferrous sulphate, whether given alone or with traces of other metals (molybdenum, cobalt, copper). Thus various authors have reported intolerance-rates ranging from 0 to 60%. Many of the reports are difficult to assess, because inadequate information on dosage, number and type of patient, and definition of intolerance is given. Some of the papers in which adequate data have been recorded are summarised in table I. If the cases given very large doses of ferrous sulphate (360 mg. of iron daily) are excluded, the incidence of intolerance in 367 patients receiving an average of 220 mg. of ferrous sulphate daily is 4%, a figure comparable to that shown in table I as occurring after the ingestion of 210 mg. of ferrous gluconate daily.

In this analysis we have not taken into account the report by Talaga (1955), because the intolerance-rate of 60% in his series of patients was conspicuously different from that reported in all other trials included in table I in which comparable doses of iron were given.

Study of the reports also shows that the iron content of the preparations of ferrous sulphate was usually larger than that of the other compounds; that the pills employed varied widely in colour, size, and type of coating; that the series of patients were not always comparable; and that the definition of "side-effects" varied from mild symptoms to a degree of intolerance necessitating cessation of treatment.

It may be assumed that the enthusiasm shown by a doctor recommending treatment, and the statements which he makes to patients about the likelihood of side-effects, will also vary. These factors can be eliminated only by arranging a trial in which pills with identical coating and the same iron content are given to matched groups of patients on the "double blind" principle—neither the patient nor the doctor knowing which preparation is being employed until after the results have been assessed.

During such a trial carried out on antenatal patients by Kerr and Davidson (1958) a comparison was made between ferrous sulphate, ferrous gluconate, and inert tablets. The incidence of gastrointestinal symptoms attributed by the patients to their pills was similar in the three groups. It was felt that pregnant women might be unsatisfactory subjects for a detailed study of this kind, because they often suffer from constipation and heartburn, and because they spend a considerable amount of time sitting in queues at antenatal clinics, discussing their symptoms. Accordingly a second double-blind trial was planned, using as subjects healthy non-pregnant young women. The results are reported here.

Plan of the Experiment

The purpose of the trial was explained to the nursing staff of the Royal Infirmary, Edinburgh, and 100 volunteers requested. Each volunteer was given six packets of pills and asked to take them, in the dosage prescribed on the packets, after meals, from Monday to Friday during six successive weeks. No pills were taken on Saturdays and Sundays, and at the end of each week a questionnaire was completed giving details of any symptoms experienced during the preceding week.

TABLE I—INCIDENCE OF GASTROINTESTINAL INTOLERANCE TO ORAL IRON PREPARATIONS REPORTED BY VARIOUS AUTHORS

Ferrous preparation	Dose (mg. iron daily)	Trace metals added	Indication for treatment	No. of patients	Intolerance-rate (%)	Author
Sulphate ..	200	Nil	Pregnancy	27	4	Devoe and Moses 1954
" ..	240	Nil	"	41	60	Talaga 1955
" ..	360	Nil	"	207	57	Gatenby and Lillie 1955
" ..	210	Nil	Hypochromic anæmia	25	13	O'Sullivan et al. 1955
" ..	360	Copper, manganese	Pregnancy	51	35	Benstead and Theobald 1952
" ..	180–240	Cobalt	"	58	0	Holly 1955
" ..	240	Molybdenum	"	75	1	Lund 1951
" ..	360	"	"	15	14	Benstead and Theobald 1952
" ..	360	"	"	91	44	Gatenby and Lillie 1955
" ..	240	"	"	24	0	Devoe and Moses 1954
" ..	240	"	"	18	6	Talaga 1955
" (white) ..	200	Nil	"	140	5	Edgar and Rice 1956
Gluconate ..	210	Nil	"	109	14	Gatenby and Lillie 1955
" ..	210	Nil	Hypochromic anæmia	25	4	O'Sullivan et al. 1955
Succinate ..	210	Nil	" "	25	4	O'Sullivan et al. 1955
" ..	105	Nil	" "	150	<1	Gillhespy 1955
" ..	105	Nil	Pregnancy	49	2	Cope et al. 1956
Calcium citrate ..	150	Nil	"	48	0	Talaga 1955

Six symptoms were mentioned specifically on the form—nausea, vomiting, heartburn, abdominal discomfort, constipation, and diarrhœa—and a space was left to record "any other symptoms". The volunteers were asked to describe only symptoms which they believed were due to the pills; they were not asked to grade their severity but merely to say whether they were severe enough to prevent their taking the full course of treatment prescribed for that particular pill. If they were obliged to stop taking one pill on account of symptoms, they were asked to continue with the others according to schedule. They were told that the first five packets contained iron pills of various types, some of which would change the colour of the stools while others would not. The sixth packet was marked "control pills" and it was explained that these were given to make sure that the coating used on the other pills was not itself a cause of symptoms.

The five "iron pills" contained: ferrous sulphate; ferrous gluconate; ferrous succinate; ferrous calcium citrate; and lactose. The last is hereafter referred to as the "unknown" control pill. The pills known to the patient as the "control" pills also contained lactose, and were identical in appearance and composition to the "unknown" control pills.

Careful consideration was given to the dosage of iron to be incorporated in the pills.

It was essential that the daily iron intake should be the same irrespective of which preparation was being taken. The usual dose of ferrous gluconate is one 300 mg. (gr. 5) pill and of ferrous succinate one 150 mg. (gr. $2^1/_2$) pill, each containing 35 mg. of elemental iron, given three times a day, making a total of 105 mg. of iron daily. The dose of ferrous calcium citrate recommended by the manufacturers is two 300 mg. (gr. 5) pills each containing 25 mg. of elemental iron, given three times a day, making a total of 150 mg. of iron per day. Ferrous sulphate, however, is usually prescribed as one 180 mg. (gr. 3) pill containing 60 mg. of elemental iron, three times a day, making a total of 180 mg. of iron daily. At the outset a decision had to be made as to whether it was desirable to increase the dose of elemental iron in each ferrous gluconate and succinate pill to 60 mg.—i.e., about double the usual therapeutic dose—or to reduce the amount of elemental iron in each ferrous sulphate tablet from 60 mg. to 35 mg. The latter choice was made because evidence had been obtained by Kerr and Davidson (1958) that ferrous sulphate was effective when given in the smaller dose.

Each ferrous-sulphate, gluconate, and succinate pill contained 35 mg. of iron; the dose of these and of the "known" and "unknown" control pills was one, three times a day. Ferrous calcium citrate could not be prepared in pills of the same size, with an iron content of 35 mg.; it was therefore made up in pills containing 17·5 mg. of iron, identical in other respects to the control pills, and given in a dose of two tablets three times a day. To this extent the ferrous calcium citrate pills were distinguishable from the others; but, with this exception, the comparison was carried out as a double blind experiment, the key being opened only after the results had been analysed. The pills were identical in size, shape, colour, and coating.

The volunteers were assigned at random to five groups which took the pills in different orders.

103 nurses volunteered. 7 failed to complete it for reasons unconnected with the pills (intercurrent illness, night duty, holidays). 3 others dropped out because they experienced unpleasant symptoms. One of these complained of abdominal pain and diarrhœa, and another of constipation, while taking ferrous sulphate. The third volunteer had various symptoms while taking ferrous calcium citrate, ferrous gluconate, and "unknown" control pills.

The 93 volunteers who completed the trial were all healthy young women aged 18–30 years (mean age 21). The hæmoglobin level was not estimated routinely, but 23 volunteers when visiting the blood clinic to collect their pills asked that this estimation should be carried out. Their hæmoglobin levels ranged from 11·7 to 15·5 g. per 100 ml. (79–105%), the mean being 13·9 g. (94%). This suggests that most of the subjects were not significantly anæmic. 11 had been treated with oral iron in the past, but none could recollect any untoward symptoms from this.

Results

The replies given by the 93 who completed the trial are summarised in table II.

In total incidence, "toxic effects" from the "unknown" control pills did not differ significantly from those accompanying any of the preparations containing iron, whether the slight or doubtful symptoms were

TABLE II—INCIDENCE OF ALL GASTROINTESTINAL SYMPTOMS IN 93 SUBJECTS WHO COMPLETED THE TRIAL

Iron preparation	1 No symptoms	2 Slight or doubtful symptoms	3 Symptoms+	4 Symptoms++	5 Total with significant symptoms (3+4)	6 Total with no significant symptoms (1+2)
Ferrous sulphate ..	58	12	22	1	23	70
" gluconate ..	69	4	17	3	20	73
" succinate ..	59	13	19	2	21	72
" calcium citrate	63	11	14	5	19	74
"Unknown" control ..	65	8	18	2	20	73
"Known" control ..	91	0	2	0	2	91

+ = symptoms definite but treatment continued. ++ = symptoms severe enough to stop treatment with that pill.

TABLE III.—INCIDENCE OF SYMPTOMS ATTRIBUTED TO IRON PILLS
(Group A: 20 subjects who complained of symptoms with "unknown" control pills. Group B: 73 subjects who did not complain)

Iron preparation	Total no.	No. with definite symptoms	Intolerance rate (%)
Group A:			
Ferrous sulphate	20	10	50
" gluconate	20	8	40
" succinate	20	5	25
" calcium citrate ..	20	7	35
Group B:			
Ferrous sulphate	73	13	18
" gluconate	73	12	16
" succinate	73	16	22
" calcium citrate ..	73	12	16

included in the analysis or not ($P>0.05$). Only 2 volunteers recorded symptoms while taking the "known" control pills; 1 complained of heartburn and 1 of constipation. When the incidence of side-effects was calculated for the whole group of 103 (using the incomplete replies of the 10 nurses who failed to complete the trial) there was again no significant difference between iron preparations and "unknown" control pills.

It was clear that factors other than iron were responsible for most of the "toxicity" reported by these volunteers. One possibility was that a proportion of them were unusually suggestible, and developed symptoms whenever they took pills which they believed to contain iron. If this were so, it would be important to exclude such subjects from consideration when comparing the iron preparations.

To test this hypothesis the 93 who completed the trial were divided into two groups—the 20 nurses who complained of symptoms with "unknown" control pills (group A), and the 73 who did not (group B). Table III shows that there was more intolerance to iron-containing pills in group A than in group B, and in the case of ferrous sulphate and ferrous gluconate this difference was significant ($P<0.05$). In group B the intolerance-rates to the four iron preparations did not differ significantly from one another.

Analysis of the individual symptoms reported with the various iron pills shows that no characteristic symptom complex resulted from taking any of the pills. With each preparation, constipation and abdominal discomfort were the commonest symptoms; the incidence of all the others was less than 10%.

11 of the subjects who did not complain of symptoms with control pills had symptoms with more than one of those containing iron. 3 of them reported constipation with each of two preparations; but otherwise there was no consistency in the symptoms of which any individual complained. Nobody reported symptoms with all four iron preparations. There was therefore no evidence of the occurrence of true iron intolerance embracing all forms of oral iron.

Discussion

The importance of psychological factors in producing both beneficial and undesirable results from drug therapy is now widely recognised.

Girdwood (1952) focused attention on this aspect of iron intolerance. In a clinical trial of molybdenised ferrous sulphate he found that many patients who were intolerant of ferrous sulphate had no symptoms when taking the preparation containing trace amounts of molybdenum. Realising that this might be partly due to the difference in appearance between the pills, he administered ferrous sulphate, in the form of white pills, to 16 patients who had previously developed gastrointestinal symptoms when taking exactly the same preparation in the form of green pills ('Fersolate'). 14 of the 16 took white ferrous-sulphate pills without complaint.

Edgar and Rice (1956) used similar white ferrous-sulphate pills in the prophylaxis of anæmia of pregnancy, and found a much lower intolerance-rate than most other investigators using the green pills.

Two main factors contribute to this finding.

Firstly, mild gastrointestinal disturbances, particularly constipation, are common in any group of young women, and particularly in the pregnant women, who in Great Britain form the majority of the patients receiving iron therapy. There is a strong tendency for the patient to attribute these symptoms to any medicine she is taking, especially if she knows that it may have such effects. This tendency may have been accentuated in the present trial since the volunteers were specifically asked to note any gastrointestinal disturbance, and their attention was directed to likely symptoms by the questionnaire. That transient incidental symptoms were responsible for many of the "toxic effects" reported is suggested by the observation that more than half the nurses who complained of symptoms with "unknown" control pills had no symptoms when taking one or other of the iron preparations.

Secondly, suggestible people can develop symptoms of psychological origin, not previously present, when taking pills which they believe will upset them.

This phenomenon is observed in most clinical trials, and the proportion of subjects who exhibit it may be surprisingly high. In a trial of phenoxybenzamine for the treatment of chilblains (College of General Practitioners 1957) 13% of the patients taking placebo pills complained of dizziness or other symptoms which they had been warned might occur with phenoxybenzamine. In a similar long-term trial of tetracycline (Moyes and Kershaw 1957) 39% of those receiving placebos complained of diarrhœa.

In the present investigation the incidence of symptoms in the group as a whole was almost the same, whether the iron was taken as ferrous sulphate, ferrous gluconate, ferrous succinate or ferrous calcium citrate. Similar "toxic effects", however, were reported equally often after taking the "unknown" control pills which were thought to contain iron but in fact contained only lactose. It is of great interest that with the "known" control pills (identical in every way with the "unknown") only 2 subjects reported symptoms. This observation may be interpreted in two ways: either (1) most of the subjects experienced no symptoms while taking the "known" control pills, or (2) the symptoms arose, but, because they could not be ascribed to the pills, were ignored or attributed to other factors.

Our impression that the "toxic effects" of the pills were not due to iron is strengthened by our finding that no symptom or group of symptoms was constantly associated with any particular preparation of iron and that, when they were on iron therapy, none of the subjects consistently complained of symptoms distinguishable from those they reported when "unknown" inert pills were taken.

It should be emphasised that the conditions in this trial were not identical with those in clinical practice.

Firstly, the dose of iron chosen for the trial approximated closely to that used in practice when commercial preparations of ferrous gluconate and ferrous succinate are prescribed, but was about half that usually employed when ferrous sulphate is prescribed. Secondly, the pills were given for only five days at a time. (This period was thought long enough for symptoms

due to gastrointestinal irritation to appear.) Thirdly, this trial differed from previous therapeutic trials in that the people taking part in it were neither anæmic nor pregnant. We would, however, point out that we obtained almost identical results in a similar trial on pregnant women (Kerr and Davidson 1958).

We conclude that a large proportion of the symptoms experienced during therapy with oral iron preparations is psychological in origin. The possibility that some patients have true iron intolerance cannot be excluded; but the incidence of toxicity—at least with doses of 35 mg. of iron three times a day—must be very low. Among those whose complaints were confined to iron preparations, the symptom most commonly reported was constipation. Other gastrointestinal effects were variable, and usually mild, and they were never reported by more than 12% of subjects.

It will take a long time to dispel the popular belief that iron pills inevitably cause unpleasant side-effects, but reassurance and enthusiastic propaganda could do a great deal to reduce the "intolerance rate". Recently we have found it well worth while to explain to patients that the pills they are about to take have been tested in a blind trial and found to cause no more symptoms than pills containing sugar.

Summary

1. Ferrous sulphate, ferrous gluconate, ferrous succinate, ferrous calcium citrate, and "known" and "unknown" control pills (containing lactose) were administered to 93 healthy young women in a double-blind trial. The incidence of gastrointestinal symptoms attributed to the pills was assessed from the replies to a questionnaire.

2. Virtually no toxic effects were reported from "known" control pills containing lactose, but the exactly similar "unknown" control pills, which were thought by the subjects to contain iron, produced as many side-effects as the pills which did in fact contain it.

3. None of the four iron compounds was found to be significantly more "toxic" than inert pills containing lactose. Hence it was concluded that intolerance to these iron preparations, in the dosage given, was mainly psychological in origin.

We wish to express our thanks to the nurses who took part in the trial and to Miss Law, assistant lady superintendent, Royal Infirmary, Edinburgh, who helped to recruit the volunteers; to Dr. Gordon Fryers, of John Wyeth and Brother, Ltd. for the supply of ferrous sulphate, ferrous gluconate, and control pills; to Mr. John Williams, of Calmic Ltd. for the supply of ferrous succinate; and to Mr. Reginald George, of Ortho Pharmaceuticals Ltd. for the supply of ferrous calcium citrate, used in the trial.

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ACCIDENTAL HYPOTHERMIA
A COMMON CONDITION WITH A PATHOGNOMONIC ELECTROCARDIOGRAM

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INDUCED hypothermia now plays an accepted part in surgery of the heart and brain and has therefore been studied a great deal by physiologists (Kayser 1957). Clinicians, however, have paid comparatively little attention to accidental hypothermia, and Rees (1958), who recently reported four cases, has stated that in clinical medicine it is uncommon.

The electrocardiogram in preoperative hypothermia has features characteristic enough to be pathognomonic (Emslie-Smith 1956, Fleming and Muir 1957). As temperature falls, the heart-rate slows and the intervals PR, QRS, and QTc all lengthen. A conspicuous extra deflection appears at the junction of the QRS complex and the ST segment. This "junction deflection" (J deflection) is slowly inscribed and is usually most obvious in lead V4, where it is directed upward. In other leads the base of the QRS complex is widened. In the vectorcardiogram these features are represented by an extra loop between the QRS and T loops (Emslie-Smith 1958). When the J deflection is large, the T wave may become inverted.

Tomaszewski (1938) published the electrocardiogram of a vagrant dying from cold. Since then the electrocardiogram in accidental hypothermia seems to have been recorded on eight occasions only (Wayburn 1947, Graybiel and Dawe 1948, Laufman 1951, Karnell et al. 1955, Biörck and Johansson 1955, Rees 1958). Only a few of these records showed the characteristic J deflection, and Rees (1958) did not see it in the electrocardiograms of his patients.

I have recently encountered eight cases of accidental hypothermia, and heard of another, in circumstances which suggest that the condition is very much commoner than is supposed. In seven cases adequate electrocardiograms showed the pathognomonic pattern; in the eighth it was obscured by bundle-branch block.

Case-reports

Case 1.—A mentally depressed woman, aged 50, was found unconscious. It was thought that she had swallowed a large dose of carbromal and barbiturate. She was cyanosed and deeply comatose, with shallow respirations occurring only three times a minute. All her tendon-reflexes were absent, her systolic blood-pressure was 60 mm. Hg, and her rectal temperature was 30·2°C (86°F).

An endotracheal tube was passed, and oxygen was given by artificial respiration with a closed circuit. An intravenous infusion of plasma was started. The electrocardiogram then showed sinus bradycardia (rate 47 a minute). Changes typical of hypothermia were present: PR measured 0·16 sec., QRS 0·08 sec., and QTc 0·57 sec.; a small, slowly inscribed, extra deflection was present between QRS and the early part of the ST segment (J deflection); it was directed upward in leads I, II, III, aVL, aVF, V4, and V6, and downward in lead aVR.

The patient died after 48 hours' coma.

Case 2.—A grossly myxœdematous woman, aged 75, was found naked and unconscious. Her heart sounds were faint, blood-pressure 150/90 mm. Hg, and respirations 20 a minute. There were no focal neurological signs. Her rectal temperature was 27°C (80·6°F). The electrocardiogram showed sinus rhythm (rate 30 a minute). It was characteristic of hypothermia: PR measured 0·19 sec., QRS 0·11 sec., and QTc 0·58 sec.; in leads aVL, V4 and V5 a small J deflection was present between QRS

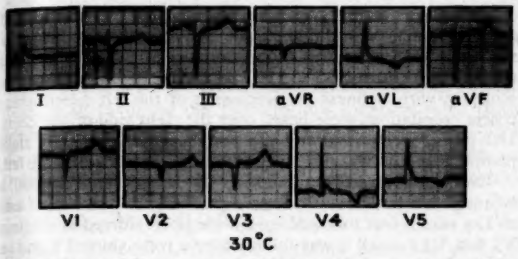

Fig 1—Electrocardiogram in case 3 with rectal temperature 30°C (86°F). Note QTc interval prolonged (0·53 sec.), typical J deflection prominent in lead V4; base of QRS widened in leads I, aVL, aVF, V5; and T inverted in leads I, aVL, V4, and V5.

and the early part of the ST segment. T was directed downward in leads I, II, III, aVF, V4, and V5, and upward in leads aVR and aVL. Despite gross myxœdema the amplitude of the complexes was not reduced: R in lead I, for example, measured 1·35 mV.

Warming and the administration of triiodothyronine were ineffective. The patient died about 12 hours after admission.

At necropsy the thyroid gland was small and fibrotic, and the plasma-cholesterol level was 550 mg. per 100 ml.; there was some hypertrophy of the left ventricle, and there was patchy atheroma of the coronary arteries without occlusion of the lumen.

Case 3.—A one-legged woman, aged 82, was found lying neglected and stuporous in front of an unlit fire. She had a black eye on the left side, and radiography showed a small fracture above the left orbit. She had multiple abrasions, and gangrene of the right foot. Her blood-pressure was 120/100 mm. Hg, and rectal temperature 30°C (86°F).

Electrocardiograms showed mechanical artefacts caused by muscular tremor. There was sinus rhythm (rate 42 a minute). The typical changes of hypothermia were present: PR measured 0·20 sec., QRS 0·05 sec., and QTc 0·53 sec.; a typical large J deflection was present in V4; T was inverted in leads I, aVL, V4, and V5; there was widening, with ledging, of the base of QRS in leads I, aVL, aVF, and V5 (fig. 1).

The patient died about 12 hours after admission. Necropsy showed ulcerating atheroma of the thoracic aorta and multiple small infarcts in spleen and kidneys. The left ventricle was hypertrophied. The cerebral cortex was slightly atrophied.

Case 4.—A diabetic man, aged 80, who was well cared for at home, began to have hypoglycæmic attacks, for which he came to hospital. His dose of insulin-zinc suspension was adjusted. Two days after discharge he behaved oddly and fell. He was put to bed and given sugar, but his manner remained peculiar all evening. At 2 A.M. he "seemed to have settled", but at 7 A.M. he was found wet, half out of bed, and without bedclothes.

He was stuporous, with corpse-like pallor and unusually

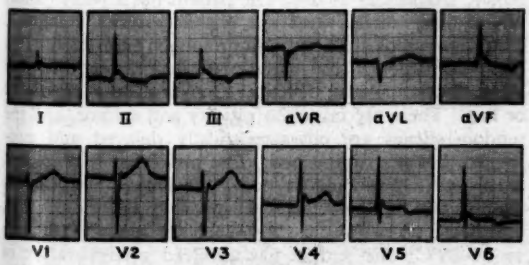

Fig. 2—Electrocardiogram in case 4 with rectal temperature 25·75°C (78·3°F). Note QTc interval prolonged (0·54 sec.), typical J deflection directed upward in leads I, II, and V2-V6 and downward in lead aVR, base of QRS widened in leads III and aVF, and T inverted in leads II, III, aVF, V5, and V6, and flat in lead I.

firm subcutaneous tissues. His blood-pressure was 115/50 mm. Hg, and his respirations were 16 a minute. His limbs were held rigid. His tendon-reflexes were all present, but his muscles contracted slowly. His rectal temperature was 25·75°C (78·3°F).

The electrocardiogram was distorted by a fine mechanical artefact caused by muscular tremor. There was sinus rhythm (rate 48 a minute). The characteristic changes of hypothermia were present: PR measured 0·24 sec., QRS 0·07 sec., and QTc 0·54 sec.; there was a conspicuous J deflection, directed upward in leads I, II, and leads V2–V6, and downward in lead aVR; T was inverted in leads II, III, aVF, V5, and V6 and flat in lead I; there was widening of the base of QRS in leads III and aVF (fig. 2).

The patient was given intravenous glucose and prophylactic penicillin and was heated under an electric blanket. 24 hours later his rectal temperature was 31·75°C (89·2°F) and his physical state more normal. His blood-sugar level was 134 mg. per 100 ml. and blood-urea level 73 mg. per 100 ml. The signs of hypothermia in the electrocardiogram were less conspicuous, but a J deflection was still present, directed upward in leads I, II, aVF, V5, and V6, and downward in lead aVR. T was inverted in leads aVF and III. The base of QRS was widened in leads III and V1.

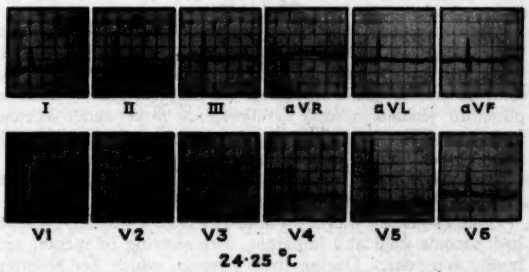

Fig. 3—Electrocardiogram in case 5 with rectal temperature 24·25°C (75·6°F). Note QTc interval prolonged (0·60 sec.), typical J deflection in leads aVF, V4, and V5, base of QRS widened in lead V6, and T flat in lead aVL and diphasic in lead V6.

About 60 hours after admission the patient's temperature was 37°C (98·6°F), pulse-rate 100, and respirations 30 a minute. Although no longer stuporous he was confused. His temperature rose to 39·5°C (103°F), and signs of bronchopneumonia appeared. Electrocardiograms now indicated anterolateral myocardial ischæmia. He died 5 days after admission.

Case 5.—Within a few weeks of beginning to live on her own, a woman, aged 72, was found lying unconscious on the floor. Relations said she had become increasingly confused and breathless and had felt the cold badly. She had occasionally been dizzy and had sometimes fallen.

She was cyanosed and comatose, with rectal temperature 24·25°C (75·6°F), and respirations 12 a minute, expiration prolonged and grunting. Her radial pulse could not be felt, and no blood-pressure could be recorded. The outer halves of her eyebrows were thin, her protruded tongue was thick, and her skin was dry and scaly. Her facial subcutaneous tissue was thick. All her limbs were rigid, but she grimaced and moved her arms slowly. Her pupils reacted sluggishly to light. Her tendon-reflexes were present, but her muscles contracted slowly. Both her legs were œdematous, with large varices.

The electrocardiogram was distorted by tremor but showed sinus rhythm (rate 36 a minute). There were characteristic changes of hypothermia: PR measured 0·24 sec., QRS 0·06 sec., and QTc 0·60 sec.; a J deflection was present in leads II, III, aVF, V4, and V5; T was flat in lead aVL and diphasic in lead V6; in lead V6 the base of QRS was widened (fig. 3).

After the patient had been warmed all night, her rectal temperature had risen to 32°C (89·6°F) and she seemed better. She answered simple questions slowly with a hoarse voice. Her systolic blood-pressure was 60 mm. Hg, and pulse-rate 62. No

cardiac murmurs were heard. The electrocardiogram showed right bundle-branch block and ventricular ectopic beats. Myxœdema was diagnosed, but despite the administration of cortisone and triiodothyronine she deteriorated and died.

At necropsy the thyroid gland was small and fibrous. There was aortic stenosis and incompetence, with left ventricular hypertrophy, and bronchopneumonia.

Case 6.—A woman, aged 81, who lived alone, was thought by her neighbours to be unwell. Her doctor found her unsteady, with slurred speech, wondered if she had taken too many sleeping tablets, and put her to bed. Next day she was found, clad only in a nightdress, confused and cold, with a black eye. On admission to hospital she was comatose, with a large contusion and laceration of the left supraorbital region. Her rectal temperature was 27·5°C (81·5°F), respirations 16 a minute, and blood-pressure 120/80 mm. Hg. Her pupils reacted sluggishly to light. Her limbs were rigid and flexed, and her tendon-jerks were present but typically slow. She had a single generalised convulsion, with conjugate deviation of her eyes to the right. Radiography showed no fracture of skull.

The electrocardiogram showed considerable clockwise rotation of a vertical heart and sinus rhythm (rate 72 a minute). The record was characteristic of hypothermia: PR measured 0·24 sec., QRS 0·04 sec., and QTC 0·49 sec.; a J deflection was present in leads II, III, and aVF; T was flat, and the base of QRS was widened, in leads V7 and V8.

After the patient had been warmed for four hours, her rectal temperature was 30°C (86°F) and atrial fibrillation was noted. Later hemiplegia and upper-motor-neurone paralysis of the seventh cranial nerve appeared on the left side. Lumbar puncture yielded normal cerebrospinal fluid under normal pressure. The patient's temperature rose to 38·3°C (101°F), signs of bronchopneumonia appeared, and she died.

Necropsy showed subdural hæmatoma in the right occipital region and atherosclerosis of the cerebral arteries.

Case 7.—Every winter for about 14 years a woman, aged 64, had become cold and lethargic, with slowing of mental and bodily activities. During these periods, which her relations described as "hibernation", she was sometimes stuporous or even comatose, and she was often admitted to hospital, where various provisional diagnoses were made and different treatments given. During a spell of cold weather in early spring she again became cold and retarded and was admitted to hospital.

She was stuporous, answering simple questions with monosyllables only. Although her eyebrows were thin, her pubic hair was thick, and she did not look frankly myxœdematous. Her skin was cold and dry, and the subcutaneous fat felt doughy. Her pupils reacted slowly to light. Her muscular tone was increased, and, although her tendon-reflexes were not increased in amplitude, her muscles contracted slowly after percussion of the tendon. Her pulse-rate was 60, and respirations were 13 a minute. The first and second heart sounds were unduly widely separated. Her blood-pressure was 118/70 mm. Hg. and her rectal temperature was 33°C (91·4°F). Her serum-cholesterol level was 420 mg. per 100 ml.; this fact strongly supported the diagnosis of hypothyoidism.

The electrocardiogram was slightly disturbed by muscular tremor and showed considerable clockwise rotation of the heart. There was sinus rhythm, with occasional ventricular ectopic beats. The typical changes of hypothermia were present: PR measured 0·18 sec., QRS 0·06 sec., and QTC 0·42 sec.; there was a prominent J deflection in leads V2, V3, and V4; T was inverted in leads II, III, aVR, aVF, and chest leads V2–V5, and flat in leads I and VI; there was widening of the base of QRS in leads I, III, and aVL.

Warming her slowly in an electric blanket raised her temperature to 37°C (98·6°F) over 24 hours, but her general condition deteriorated, and she became comatose, with blood-pressure 80/50 mm. Hg. Treatment with triiodothyronine and cortisone produced a steady improvement, but she developed pyrexia and signs of bronchopulmonary infection and died a week after admission.

At necropsy the thyroid gland was small (10 g.), the heart was dilated, and there was focal acute and chronic pancreatitis.

Case 8.—A woman, aged 86, who lived alone, was noticed to be confused. Next day she was found comatose, with shallow respirations 16 a minute, blood-pressure 50/30 mm. Hg, and rectal temperature 26·5°C (79·7°F). She had severe kyphoscoliosis, with dullness on percussion of the left hemithorax; coarse crepitations were heard over the right side of her chest. Her pupils were small and did not react to light. Her right plantar response was flexor; there was no response on the left.

The electrocardiogram showed sinus rhythm (rate 30 a minute). PR measured 0·44 sec., QTC 0·61 sec. In leads I and aVL a tiny R was followed by a wide deep slurred S. In lead V1 and V2 a small Q was followed by a wide slurred R and an inverted T; in leads V5 and V6 a large R was followed by a deep wide slurred S and upright T. These findings were interpreted as evidence of right bundle-branch block, possibly with anteroseptal infarction. However, lead V3 showed a small R, then a rounded larger deflection which might have been a J deflection; T was inverted. Lead V4 showed a larger R followed by a smaller rounded deflection (possibly J) and an inverted T. Leads aVF and III showed what would have been interpreted, in the absence of right bundle-branch block, as the J deflection and inverted T of hypothermia.

Warming was begun, but the patient died a few hours after admission.

Discussion

In patients made hypothermic before operations on the heart or the brain a temperature of 28–30°C is achieved by elaborate medication and cooling. Seven of my patients with accidental hypothermia had rectal temperatures between 30·2°C and 24·25°C (mean 27·2°C, s.d. 2·2).

Six of the patients were admitted to hospital within two winter months, and in all of them accidental hypothermia was diagnosed by physicians who had already taken special interest in the subject. In none of the patients, however, was the actual depth of hypothermia appreciated until the accurate rectal temperature was taken by a laboratory thermometer or a thermistor recorder. These facts suggest that the condition is very much commoner than is generally supposed, and that it is often unrecognised despite distinctive clinical features and a pathognomonic electrocardiogram.

Rees (1958) has stated that hypothermia is a hazard of the extremes of life, and it is significant that, if the case of suicide is excluded, the mean age in this series was 77 (S.D. 6·9). Five of the patients lived alone, and this fact, too, is important, although case 4 shows that hypothermia can develop rapidly even without neglect. It is clear from the case-reports that a British bedroom in winter is cold enough to make an elderly person with impaired cerebral function severely hypothermic, especially if he lies wet and partly clad.

The clinical effects of hypothermia in man are characteristic (Alexander 1946). The patient has a waxy pallor, but the superficial veins are not necessarily collapsed. The respirations are slow, with prolonged expiration. The heart beats slowly, the blood-pressure may be low, and atrial fibrillation may develop. Consciousness is clouded or lost. There are muscular rigidity and tremor, and the tendon-reflexes are characteristically delayed and prolonged, but not diminished. The pupils are dilated, and their reaction to light is poor. At lower temperatures rigidity and tendon-reflexes disappear, respiration ceases, and death takes place usually when the temperature falls to 24–26°C; one patient has survived a temperature of 18°C (Laufman 1951). Most of the features were present in all my patients. Although shivering was not often evident clinically, a fine muscular tremor produced an almost constant mechanical artefact in the electrocardiogram.

It is important to recognise the clinical picture of

hypothermia because it may disguise that of the underlying condition and thus delay full diagnosis and adequate treatment.

The changes in the electrocardiogram found in various degrees in seven of my patients are identical with those constantly found in induced hypothermia in patients with normal hearts (Emslie-Smith 1956) and analogous to those seen in experimental hypothermia in dogs (Emslie-Smith et al. 1958). The lengthening of the RR, PR, QRS, and corrected QT (QTc) intervals, the presence of the typical J deflection, with or without inversion of T, in leads related to the left ventricle, and the widening of the base of QRS in other leads, together constitute a pathognomonic pattern. The J deflection is almost always most conspicuous in left chest leads, especially lead V4. If adequate electrocardiograms with chest leads are not recorded, the J deflection may be missed; this is probably why it has not previously been recorded in accidental hypothermia with any constancy.

Atrial fibrillation developed at a mean temperature of 28·9°C in six of ten patients with normal hearts during the production of preoperative hypothermia (Emslie-Smith et al. 1958). By contrast it developed in only one of the eight cases of accidental hypothermia.

The finding of the typical pattern in the electrocardiogram of a stuporous patient should suggest hypothermia. Thus in case 3 the diagnosis was initially made from an electrocardiogram recorded to exclude a cardiac infarct or heart-block. It is, of course, easier to take the rectal temperature with a laboratory thermometer than to record the electrocardiogram, and probably the best way to diagnose accidental hypothermia is to remember the fact that it may complicate any state of impaired consciousness in an elderly patient.

Summary

Accidental hypothermia has recently been diagnosed nine times in elderly patients in circumstances which suggest that it is much commoner than is generally supposed.

The electrocardiogram showed a pattern pathognomonic of hypothermia in seven of the eight cases in which it was recorded: in the eighth case the typical features were masked by bundle-branch block.

The RR, PR, QRS, and QTc intervals were lengthened. The characteristic J deflection of hypothermia was present in leads related to the left ventricle; when it was conspicuous, T was sometimes inverted. In other leads the base of QRS was widened. These changes were identical with those constantly seen in induced hypothermia in patients with normal hearts and analogous to those found in experimental hypothermia in dogs.

Failure to use adequate leads, especially left chest leads, probably explains why this pathognomonic pattern has not been constantly found in accidental hypothermia.

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TRIAMCINOLONE

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SINCE the clinical use of the Δ^1 analogues of cortisone (prednisone and prednisolone) was first reported by Bunim et al. in 1955, further efforts have been made to produce analogues which would have equal or greater efficiency as anti-inflammatory agents but fewer unwanted effects, particularly gastroduodenal ulceration. The advantage of the Δ compounds was that they caused less salt and water retention than cortisone or hydrocortisone, while being clinically effective in approximately a fifth of the dose. It was not long before new compounds appeared, and at the 9th International Congress of Rheumatology in Toronto last year the clinical effects of two more were reported—namely, triamcinolone (16-α-hydroxy, Δ^1, 9-α-fluorohydrocortisone) (fig. 1) by Freyberg et al. (1957) and medrol (6-methyl prednisolone) by Boland and Liddle (1957). The former substance is the subject of this report.

Fried (1955) found that substitution of a fluorine or chlorine atom at C9 in the hydrocortisone molecule produced an increase in the glucocorticoid action and a greater increase in mineralocorticoid or sodium-retaining effect. Apart from external application for skin disorders, this substance, 9-α-fluorohydrocortisone (fludrocortisone), is now used only in salt-losing cases of Addison's disease or after adrenalectomy. In 1953 Hirschmann et al. reported that, by adding a hydroxyl group to deoxycortone (DOCA) at C16 in the α position, the characteristic salt-retaining activity of this substance was eliminated. Three years later Bernstein (1956) reported that by adding a 16-α-hydroxyl group to the powerful 9-α-fluorosteroids their sodium-retaining potency was lost without decrease of glucocorticoid activity. Addition of the 16-α-hydroxyl group not only failed to produce sodium retention, but actually caused sodium excretion and diuresis while glucocorticoid activity was retained. This particular virtue did not impress us as constituting a great clinical advance on prednisone or prednisolone, except perhaps for patients with cardiac decompensation who were unable to tolerate the former substances. What interested us more was the suggestion in early reports that certain side-effects—i.e., peptic ulceration, mental disturbances, and osteoporosis—were less with triam-

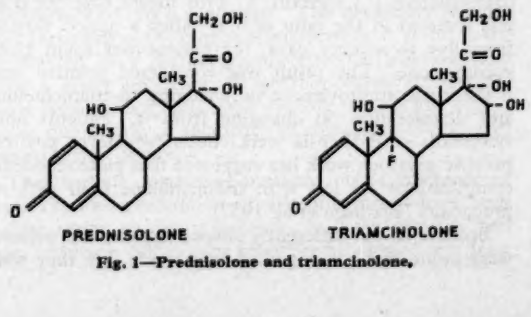

Fig. 1—Prednisolone and triamcinolone.

EFFECT OF TREATMENT WITH TRIAMCINOLONE COMPARED WITH THAT OF PREDNISOLONE

Case no.	Sex	Age (yr.)	Length of history	Subjective pain and stiffness *	Grip	Finger swelling	Indigestion	Comment
1	F	60	4 yr.	90	+50%	+9	Much improved	—
2	F	37	3 yr.	90	+35%	+3	Nil	—
3	F	60	5 yr.	50	+25%	Unchanged	Much improved	—
4	M	60	13 yr.	100	Unchanged	,,	Nil	—
5	M	44	5 yr.	100	,,	,,	Disappeared	Indigestion returned with prednisolone
6	F	54	16 yr.	100	,,	,,	Nil	Postprandial flushings
7	M	55	6 mos.	50	,,	,,	Nil	—
8	F	44	18 mos.	120	,,	,,	Worse	Better on prednisolone
9	M	70	1 yr.	100	,,	,,	Nil	—
10	F	39	10 yr.	90	,,	+8	Nil	—
11	F	66	1 yr.	100	+15%	Unchanged	Nil	—
12	M	63	9 yr.	100	Unchanged	,,	Nil	—
13	F	62	6 yr.	100	,,	,,	Unchanged	Postprandial flushings
14	F	44	3 yr.	80	,,	+5	Nil	—
15	F	45	4 yr.	100	,,	Unchanged	Nil	—
16	F	60	2 yr.	80	,,	,,	Nil	Diabetes worse on triamcinolone
17	F	58	5 yr.	90	,,	,,	Nil	Less swelling of previously thrombosed leg
18	M	71	8 yr.	100	,,	,,	Nil	—
19	F	45	5 yr.	100	,,	,,	Nil	Postprandial flushings
20	M	48	3 yr.	100	,,	,,	Worse	—
21	F	35	1 yr.	50	,,	,,	Nil	—
22	M	40	1 yr.	120	,,	,,	Nil	—
23	F	38	1 yr.	50	+20%	+19	Nil	Indigestion with prednisolone
24	M	55	10 yr.	125	Unchanged	Unchanged	Worse	—
25	M	50	4 yr.	50	,,	,,	Nil	Psoriatic arthropathy: psoriasis much improved

* Assuming that the symptoms on prednisolone are 100%. Finger swelling is measured by jewellers' rings and recorded as + if reduced. Figures given are an average of all estimations.

cinolone than with prednisolone. The dyspeptic rheumatoid is one of the most difficult patients to treat, and any reduction in the incidence of peptic ulceration as a complication of therapy would be very welcome.

The first clinical reports of Freyberg et al. (1957) and Hellman et al. (1957) showed little difference between the anti-rheumatoid properties of triamcinolone and prednisolone though the former appeared slightly more potent, 4 mg. giving much the same therapeutic effect as 5 mg. of prednisolone. For this reason triamcinolone is usually made in 4 mg. tablets whereas prednisolone tablets are 5 mg. Sherwood and Cooke (1957) thought the ratio of efficacy in bronchial asthma was about 2/1 in favour of triamcinolone.

We therefore set out to answer only two questions in this short-term pilot trial:

(1) Is triamcinolone in a dose ratio of 4/5 as good as, better than, or inferior to prednisolone as a therapeutic agent in rheumatoid arthritis?

(2) Is it less irritating in dyspeptic patients who have symptoms suggestive of peptic ulceration?

We did not attempt to assess osteoporotic or mental differences in the two treatment groups.

Scheme of Trial

The aim was to compare triamcinolone with a previously known and well-tried steroid, and for this purpose prednisolone was selected. The trial was conducted in the same way as our previous short-term study (Hart, Clark, and Golding 1955) comparing the effect of cortisone with prednisolone or prednisone on rheumatoid arthritis.

In the present trial patients were given prednisolone until improvement was maintained at a constant level, and then this was changed to the same number of tablets of triamcinolone ('Ledercort'). This meant that the dose was reduced in the ratio of 5/4. After a period varying from five to seventy days, the patient was again given prednisolone. The result was considered positive only if there was improvement on changing to triamcinolone and deterioration on changing from it. Patients with symptoms of dyspepsia were chosen whenever possible because previous work has suggested that gastroduodenal complications are less with triamcinolone than with its precursors (Berntsen et al. 1957).

Because of the differently shaped tablets, the patients were aware that a change had been made, but they were told that the new tablets were almost identical with the old, and no preference or enthusiasm was shown for them by members of the staff. All patients were already keeping a daily record of pain, stiffness, the number of analgesic tablets consumed, and the length of time it took them to loosen up in the early morning (known in the ward as the L.U.T. or limbering-up time). Records were made by the same medical observer every three to four days of joint tenderness in the fingers, finger swelling, and strength of grip. Erythrocyte-sedimentation rates (Westergren) were taken weekly.

Results

Rheumatoid Arthritis

24 patients with rheumatoid arthritis and 1 with psoriatic arthropathy were treated in the way described above and the results are shown in the table. In no case

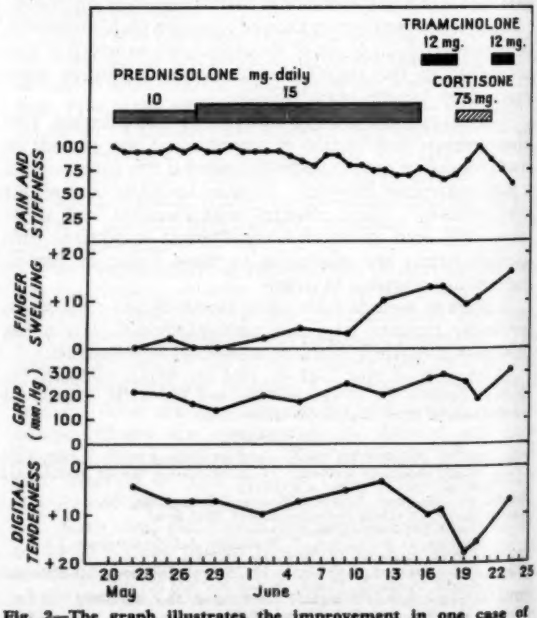

Fig. 2—The graph illustrates the improvement in one case of rheumatoid arthritis on changing from prednisolone to triamcinolone, with deterioration on changing to cortisone and further improvement with return to triamcinolone.

was there any significant alteration in sedimentation-rate or finger tenderness. In 11 patients subjective estimation of pain and stiffness was unchanged, 3 improved on prednisolone, and 11 on triamcinolone, but in only 5 was the improvement with triamcinolone more than slight. Grip measurement was unchanged in all but 5 who improved on triamcinolone. Finger swelling was also unchanged except in 5, who also improved on triamcinolone. 7 patients had indigestion; in 3 it improved on triamcinolone, in 3 it became worse, and in 1 it was unchanged. There were no acute "rebound" symptoms on transfer from prednisolone to triamcinolone or vice versa. No significant weight changes occurred with either drug, though 1 patient had a consistently increased urinary output on triamcinolone, and 1 noticed diminished swelling not only in the affected joints but also in a swollen (previously thrombosed) leg. In the case of psoriatic arthropathy the skin condition improved only with triamcinolone, and then strikingly. 1 diabetic passed more sugar on triamcinolone than on prednisolone, and the blood-sugar level rose with triamcinolone. 3 patients noticed hot feelings in the face and neck after meals only when taking triamcinolone. In 2 patients who had had prednisolone for over two years, large striæ appeared on the abdomen within fourteen and twenty-one days of changing to triamcinolone. Our patients on triamcinolone did not complain particularly of anorexia, headache, and lassitude, which have been reported by other observers. About half the patients preferred triamcinolone to prednisolone, but the difference was slight except in 5. This may have been partly because a differently shaped tablet gave the impression of a new form of therapy. Patients with rheumatoid arthritis are an optimistic group. 3 cases are of particular interest:

Case 26.—A woman, aged 58, with a thirteen-year history of rheumatoid arthritis, had had steroid therapy for six years. Recently, on prednisone 5 mg. q.d.s., vascular-necrotic lesions appeared on the hands and feet. On May 5, 1958, she was given triamcinolone 4 mg. q.d.s., with an estimated subjective improvement of 15%. A week later she had an episode of vomiting, possibly dietetic in origin, and was put back on to prednisone. On May 24 triamcinolone 4 mg. t.d.s. was again substituted, and in the early hours of May 29 a gastric ulcer perforated. During operation, which was successful, she had intramuscular cortisone in high dosage, and she has since remained well on oral hydrocortisone 60 mg. daily.

Case 27.—A housewife, aged 54, developed severe and disabling rheumatoid arthritis in 1954. Cortisone 75 mg. daily produced some improvement initially, and she has taken steroids ever since. Her condition has gradually deteriorated though there was a temporary improvement when prednisolone was given in 1955. A year later a lumbar vertebra collapsed because of osteoporosis; meanwhile a moon-face was becoming more noticeable. In April, 1958, triamcinolone 12 mg. daily was substituted for 15 mg. of prednisolone. Since then her moon-face has become worse, and prominent striæ have appeared on the flanks and both breasts.

Case 23.—A woman, aged 38, with four months' history of acute rheumatoid arthritis was treated in hospital with prednisolone 5 mg. b.d., and improved greatly. Five months later she became pregnant, and the rheumatoid arthritis worsened steadily in spite of increase of prednisolone to 17·5 mg. daily, which caused mild indigestion. She was again admitted to hospital and after a week there was little improvement. Triamcinolone 14 mg. daily was started, and during the next week there was a 50% improvement in her general condition, with a 25% increase in grip and reduction in finger swelling by 19 ring sizes. The indigestion subsided.

Comment.—This case illustrates the definite improvement in some patients who are transferred to triamcinolone. Pregnancy apparently caused this patient's relapse. This is the reverse of what is usually seen, but such cases are not uncommon.

Systemic (Disseminated) Lupus Erythematosus

3 patients with systemic lupus erythematosus have been treated for periods of two to eight weeks on triamcinolone.

Case 28.—In 1949 a housewife, now aged 55, developed what was thought to be rheumatoid arthritis. Cortisone therapy was begun two years later. In 1954, following its abrupt withdrawal, she became acutely ill, with vomiting, abdominal pain, and fever, and lupus erythematosus cells were found in the blood. There was a good response to prednisolone, which she took throughout 1957—usually 15 mg. daily in divided doses—but there were several episodes of vomiting when it became necessary to increase the dose. Despite rigid salt restriction, she gradually became moon-faced and hypertensive.

At the end of 1957 she developed severe and persistent back pain. In February, 1958, X-ray films of the spine were satisfactory, and her daily dose of prednisolone was increased to 25 mg. Two months later it was reduced gradually to 15 mg. daily, and then triamcinolone 12 mg. daily was substituted. Her back pain, however, became worse, and in May there was gross radiographic osteoporosis, with crush fractures of vertebræ and fractured ribs. She has now had triamcinolone for eight weeks; her face is becoming more moon-like and striæ have appeared on her flanks.

Comment.—The osteoporosis was probably associated with increased prednisolone dosage. There is no evidence that triamcinolone is alleviating the features of Cushing's syndrome; and it may be making them worse.

The treatment of 2 other patients with disseminated lupus erythematosus has also been changed from prednisolone to triamcinolone and back to prednisolone without any significant alteration in their condition.

Ulcerative Colitis

In 2 patients with ulcerative colitis 12 mg. of triamcinolone daily was substituted for 15 mg. of prednisolone. Triamcinolone was continued for a week, and then prednisolone was given again. In both cases the patients' subjective wellbeing, the number of stools and their consistence, and the amount of bleeding remained unaltered.

Discussion

On the results of this short-term survey there seems little to choose between triamcinolone and its predecessors in the treatment of rheumatoid arthritis. In our small series there was no real difference in aggravation or amelioration of dyspeptic symptoms, for 3 patients improved and 3 worsened when given triamcinolone. The most important of all the so-called side-effects of steroid therapy—namely, dyspepsia with or without peptic ulceration—is not a fundamental or common feature of idiopathic Cushing's syndrome. The possibility remains that variations of the cortisone molecule may result in the production of a therapeutically effective glucocorticoid with a lower incidence of gastroduodenal side-effects. Long-term studies will reveal whether there is any appreciable diminution in incidence of these side-effects with triamcinolone or not.

Two serious reactions—multiple crush fractures of vertebræ, and perforation of a peptic ulcer—were seen in our series on triamcinolone. As both patients had been receiving full dosage with prednisolone for a long

time before, one cannot say which steroid was particularly at fault, though in the former the period of increased prednisolone dosage was probably responsible.

What then are the advantages, if any, of this new substance? Triamcinolone is another effective steroid with no particular virtue except that it does not cause salt and water retention. It appears to have certain mild side-effects unlike those seen with the previous Δ compounds; but, apart from postprandial flushing, these were not seen in our present small, short-term series. The incidence of serious side-effects will have to be assessed on larger numbers.

Where there was any advantage in changing from one drug to another it usually lay with triamcinolone, but the difference was small. In a few cases objective physical signs improved on triamcinolone, but again the differences were usually slight.

Summary and Conclusions

The treatment of 24 patients with rheumatoid arthritis and 1 with psoriatic arthropathy was changed from prednisolone to triamcinolone and (after a period of five to seventy days) back to prednisolone. The dose ratio of triamcinolone to prednisolone was 4/5. Of these 25 patients, 11 preferred triamcinolone to prednisolone, 3 preferred prednisolone to triamcinolone, and 11 were indifferent.

Measurement of sedimentation-rate and digital tenderness remained unchanged. Finger swelling and grip strength altered in only 5 patients, each of whom improved on triamcinolone.

There were no acute "rebound" symptoms on changing to either drug. In only 5 cases was subjective improvement more than slight—in each case in favour of triamcinolone.

Of 7 patients who complained of dyspepsia on prednisolone, 3 improved when transferred to triamcinolone, and 3 deteriorated.

In 3 cases previously treated with prednisolone for over two years abdominal striæ appeared within three weeks of changing to triamcinolone. 3 patients noticed postprandial flushing on triamcinolone, but not on prednisolone.

The case-histories are presented of 3 patients with rheumatoid arthritis and 1 with systemic lupus erythematosus. 2 others with the latter disease and 2 with ulcerative colitis were given triamcinolone without any change in their condition.

Although triamcinolone does not differ greatly in its therapeutic action or in its undesirable side-effects from prednisolone it is useful to have another effective steroid available.

Our thanks are due to the Lederle Laboratories Division of the American Cyanamid Company for supplies of triamcinolone ('Ledercort').

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TRIAMCINOLONE ARTHRITIS?

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TRIAMCINOLONE was synthesised by Bernstein et al. (1956). Early clinical studies have shown it to be therapeutically active in many conditions previously known to respond to cortisone, prednisone, and prednisolone (Hellman et al. 1957, Sherwood and Cooke 1957, Rein et al. 1957), and its therapeutic potency has been assessed as twice that of prednisolone (Sherwood and Cooke 1957).

When a supply of triamcinolone became available in Singapore, its clinical value was assessed in fourteen patients with various different conditions requiring corticosteroid maintenance therapy. All had been receiving optimal doses of prednisolone, as determined by trial and error, with individual adjustments to give the best therapeutic response without producing any important side-effects. Three of these patients had rheumatoid arthritis and two had systemic lupus erythematosus. None of the others had ever noticed pain or stiffness in their joints; yet three of them developed arthritis, apparently as a result of the administration of triamcinolone. This complication has not been described previously.

Case-reports

Case 1.—A European woman, aged 23, had thrombocytopenic purpura. She gave a 3 months' history of bruising and of menorrhagia. Her hæmorrhagic diathesis responded well to prednisolone therapy, but a daily dose of 5 mg. was necessary. The only objective side-effects of this treatment were pronounced hirsutism and slight acne, but on questioning she stated that her libido was increased and orgasms were facilitated.

After 6 months prednisolone was stopped and she was given triamcinolone 2 mg. daily. Within 24 hours she developed "flitting rheumatic pains" in her left shoulder, right elbow and wrist, and both feet. She had no fever, tachycardia, or excessive sweating. The erythrocyte-sedimentation rate (E.S.R.) was 5 mm. (Westergren). The administration of triamcinolone was continued and she was given codein. co. *B.P.* 2 tablets every 4 hours. The pains decreased over the next 2 days and the analgesic tablets were discontinued. After a month on triamcinolone her fingers showed swelling, typical of early rheumatoid arthritis, around the metacarpophalangeal and proximal interphalangeal joints. The range of movement of her shoulder, knee, and elbow joints were all diminished. The E.S.R. was still 5 mm. During the same period the thrombocytopenia recurred and she again began to bruise easily.

When triamcinolone was replaced by prednisolone 10 mg. daily, the swelling and stiffness of her joints rapidly disappeared, the thrombocyte-count increased, and she ceased bruising easily.

Case 2.—An Indian girl, aged 17, had 6 years' history of progressive bronchial asthma. She was stunted and pigeon-chested. Initial treatment with cortisone produced a definite improvement, but if the dose was reduced below 100 mg. daily she had severe asthmatic attacks. She developed a moon-face and mild hypertension of 135/90 mm. Hg. After 6 months the cortisone was replaced by prednisolone, initially 20 mg. daily, but it was possible to reduce this to 10 mg. daily over a period of 7 months without precipitating asthma. During this period she grew 3 in. taller, gained 12 lb. in weight, and developed a good physique. Her blood-pressure fell to 125/80, but her facial rounding remained. She also developed acne and hirsutism, and noticed that her clitoris was enlarging.

Prednisolone was replaced by triamcinolone, and on a daily dose of 4 mg. she remained free of serious asthma for 4 weeks; but after 5 or 6 days she began to develop severe pains in her arms and legs, and noticed that her fingers were becoming stiff.

Her right leg was particularly painful and examination revealed a tender nodule in the lateral head of the gastrocnemius. Her fingers showed swelling of the proximal and middle phalangeal joints, and the movements of her wrists, elbows, shoulders, hips, and knees were all limited by pain.

The triamcinolone was stopped and she was again given prednisolone 10 mg. daily. The joint pains and stiffness disappeared in 2 days and a week later her fingers were normal.

Case 3.—An Indian woman, aged 21, had a 5-year history of bronchial asthma. This was controlled by cortisone 100 mg. daily, but, during 7 months' holiday in India, her weight increased from 103 lb. to 164 lb. (height 63 in.) and she developed a very pronounced moon-face, slight dependent œdema, and a blood-pressure of 130/90 mm. Hg. On a slimming regime and replacement of cortisone by prednisolone 10 mg. daily, she slowly lost weight, her face became thinner, and her blood-pressure fell to 120/80. Her asthma was controlled by this dose, but she developed severe acne and hirsutism. Another complication was a vulval abscess, which responded to penicillin. It was found that her clitoris was unusually large.

Prednisolone was replaced by triamcinolone, and on a daily dose of 4 mg. she remained free of asthma for 7 weeks. After 5 weeks, however, she complained that her legs seemed weak and she had pain in her knees. No objective evidence of arthritis was found, but, when the triamcinolone was stopped and she started on prednisolone again, the pain and weakness ceased.

Discussion

The onset of arthritic symptoms in three out of nine patients (who had no previous history of arthritis) when treated with triamcinolone instead of prednisolone strongly suggests that the change of therapy was responsible. The first two patients developed the typical appearances of early rheumatoid arthritis, and no other predisposing cause, such as infection or climatic change, was evident. All three were young women whose previous prednisolone therapy had produced virilising side-effects, and this may be significant. Two other women showing these side-effects, one with advanced rheumatoid arthritis and the other with systemic lupus erythematosus, had severe exacerbations of their joint symptoms when given triamcinolone; but this might have been merely due to inadequate dosage with corticosteroids, which often produces such relapses.

Possibly the arthritic symptoms in these three patients were primarily the result of prednisolone withdrawal. This seems unlikely since the use of prednisolone in many conditions in Singapore has not precipitated such symptoms, unless the patients had arthritis before the initial administration of corticosteroids. The remaining possibility is that triamcinolone directly caused an arthritic syndrome resembling, if not identical with, rheumatoid arthritis. It would be interesting to give the three patients another course of triamcinolone, to see whether they again develop arthritis; but they have not agreed to such a trial, and this unexpected finding must await further confirmation before its true significance can be assessed.

Apart from the development of arthritis, the results of triamcinolone therapy in this small series of patients were highly promising. In some cases its therapeutic efficiency was superior to that of prednisolone. The potency of triamcinolone was usually greater than that of prednisolone, though there was considerable variation in the equivalent dosages of the two corticosteroids in different patients.

Summary

Fourteen patients, previously maintained on prednisolone therapy for various conditions, were given triamcinolone. Of nine with no previous history of joint symptoms, three developed arthritis, and their histories are reported.

In two patients the condition resembled acute rheumatoid arthritis. It is suggested that arthritis may be a side-effect of triamcinolone therapy.

I am grateful to the Lederle Laboratories Division of the American Cyanamid Company for providing the triamcinolone ('Ledercort').

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SLIPPING OF THE UPPER FEMORAL EPIPHYSIS

A PLEA FOR URGENCY

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UNTIL recently the standard treatment of slipping of the upper femoral epiphysis was often traction in bed for six months or more. This gave relief from weightbearing; but in a large proportion of patients it did not achieve reduction. In a few cases the deformity even increased. In addition, at the end of this period the limbs were so weak, and sometimes so stiff, that they could ill support a heavy child whose weight had not decreased while lying in bed. Fusion across the epiphyseal line had been accelerated, but only at the expense of strength and function.

Surgical Treatment

Before 1929 this condition had frequently been treated by manipulation and plaster immobilisation; but a paper by Carnitz, which showed the results of manipulation, brought a sharp change in policy.

In 1938 Wilson, of the Hospital for Special Surgery, New York, described good results in 9 cases in which a Smith-Petersen pin had been inserted across the epiphyseal line. This operation produced equally good results in other clinics, so that internal fixation became accepted as a standard treatment for minor degrees of slip. The method has the limitation that it cannot be used when the displacement exceeds one-third of the maximum; but, with this proviso, it is a valuable procedure. It immediately stabilises the epiphysis; it prevents further slipping; and it accelerates fusion at a favourable age and at a level where interference with limb length is not serious.

With proper technique the operation is simple to perform: and the patient has to be immobilised for no longer than it takes the wound to heal. A child can return to school after three weeks. More recently Smith-Petersen's trifin nail has been criticised as being unnecessarily large and traumatic: and Hall (1957) has shown that smaller pins are equally effective and less likely to damage the vessels of the upper end of the femur.

Once the epiphysis has become dislodged, it is liable to go on slipping. Minor slips can be dealt with easily and satisfactorily, but major ones, if irreducible, have a very different prognosis. Left alone, these hips develop an adduction and external-rotation deformity; their range of movement will diminish; and there will be shortening and

Fig. 1—Severe, irreducible deformity.

Fig. 2—Osteoarthritic changes of untreated adolescent coxa vara.

liability to premature osteoarthritis (figs. 1 and 2). To such inactive treatment surgery is the only alternative: but none of the operations employed is uniformly satisfactory.

Groups of Patients

In the first group are adolescents with minor slips. They should be regarded as surgical emergencies. Immediately the condition is diagnosed the patient must cease to bear weight, and the surgeon must not rest content until the epiphysis is safely stabilised by pinning. Once this has been done, it may be justifiable to assume that the hip-joint has been saved.

Patients with acute traumatic displacement comprise the second group. They should be treated by immediate reduction and simple pinning. Provided that treatment is started while the epiphysis is still mobile, replacement is not difficult. A difficult manœuvre—where force has to be used—is liable to damage further the already precarious blood-supply; and this may lead to stiffening. Reduction is obtained by traction in internal rotation for two or three days, followed by gentle replacement under a general anæsthetic.

The third group of patients are those who have a severe, irreducible deformity. They all started in the first or second group but they were either not recognised or not treated in time.

Causes of Delay

It was the long interval between the onset of symptoms and the beginning of surgical treatment which prompted me to refer to the notes of 45 cases treated under my care during the past ten years. From this review two significant facts emerged. The average time between the onset of symptoms and the diagnosis was 26·6 weeks. The average time between diagnosis and admission for definitive treatment was 3·8 weeks. (This second figure includes the time spent by some patients undergoing treatment by bed rest and traction before their transfer to an orthopædic unit for pinning.)

The causes of the delay were as follows:

1. Failure of the patient to recognise and report symptoms.
2. Failure of parents, schoolteachers, or games staff to recognise and report symptoms.
3. Delay in clinical diagnosis.
4. False radiological reassurance.
5. Lack of realisation of the urgency of treatment by the referring doctor, or by the hospital clerical or surgical staff.

It is unlikely that anything can be done to shorten the delay which is due to the adolescent not reporting his symptoms. They are often slight; and his attitude is understandable, even admirable. Failure of the parents or of the school staff to appreciate the significance of such symptoms is also understandable: the condition is so uncommon and so difficult to recognise that it would be inappropriate to burden the public with medical propaganda for wider recognition. It is unfortunate that by far the greatest delay occurs for these two reasons.

Delay in Clinical Diagnosis

Even to the clinician, however, slipping of the epiphysis may be a difficult diagnosis. It affects two types of patients, the fat type with hypogonadism and the long-limbed type who is passing through a phase of rapid growth. It is slightly more common in boys. In girls the commonest age of onset is twelve, and in boys thirteen; but the trouble may start at any time between nine and cessation of growth.

The symptoms are invariably pain, a limp, or both. The pain is sometimes localised to the hip; but more often it is referred to the lower anterior part of the thigh, or to the knee. There is generally no other complaint: and the patient may have continued to play games, however strenuous. Examination of the hip will show limitation of abduction, of flexion, and of internal rotation, depending on the degree and the direction of the slip.

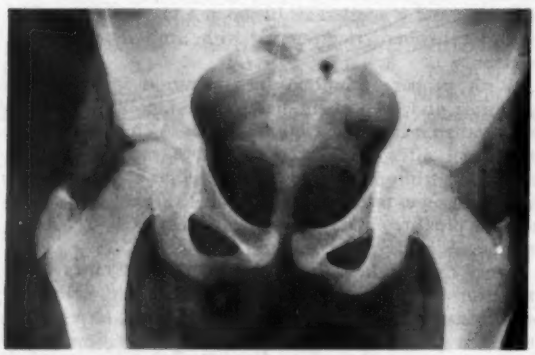

Fig. 3—Anteroposterior view of hips, showing very little evidence of slip on right side.

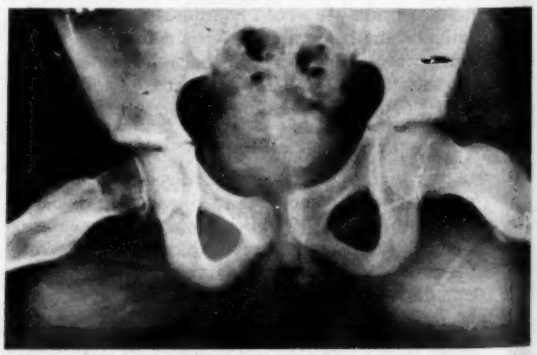

Fig. 4—Same case, showing undoubted slip of right femoral epiphysis.

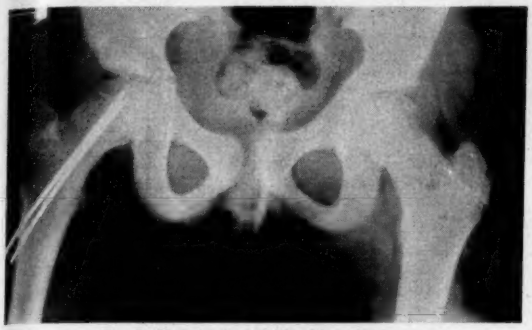

Fig. 5—Epiphysis stabilised by pinning.

In severe cases there will be considerable flexion, adduction, and external-rotation deformity with true and apparent shortening. The great trochanter will be displaced towards the pelvis. It is rational to submit any child or adolescent who complains of pain in the hip or knee to X-ray examination of the hip-joints.

Delay in Radiological Diagnosis

In a surprising number of cases referred for X-ray examination normal results are returned. In this series such false radiological reassurance was the cause of delay in 7 cases. Omission to take a lateral view was the reason for the mistake. Often an anteroposterior view will show very little abnormality, whereas a lateral view will clearly demonstrate early slipping (figs. 3–5).

The Urgency

Even when the condition is suspected or diagnosed, the urgency of treatment is often not recognised. There may be delay in referring the patient to the appropriate clinic, or a distant appointment may be accepted by the practitioner or by the receiving-room or clinical staff.

Slipping of the upper femoral epiphysis should be recognised as a surgical emergency; and admission to hospital should be immediate. Modern operative treatment gives excellent results in early and acute traumatic cases, often necessitating a stay in hospital of no longer than three weeks. Delay makes the prognosis much worse.

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THE SYNDROME OF THE SUSPENDED HEART

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THE occasional finding of abnormal electrocardiograms in patients without manifest cardiac disease may cause much difficulty in assessment of these subjects. Without necropsy evidence of a strictly normal myocardium one cannot with assurance state that the electrocardiographic disturbance is not associated with heart-disease. However, Evans and Lloyd-Thomas (1957) have, under the title of "The syndrome of the suspended heart," presented convincing evidence of the association of certain specific electrocardiographic "abnormalities" with a particular radiological configuration of the heart. Briefly, the electrocardiograms show abnormal S-T segments and T waves suggesting infarction of the lateral and postero-inferior portions of the left ventricle, or of left ventricular strain without abnormal voltages. Radiological examination shows a heart that, during deep inspiration, appears to be suspended between the vascular pedicle above and the inferior vena cava below.

We report here three cases of this syndrome seen by us in private practice since the publication of the article by Evans and Lloyd-Thomas (1957).

Case-reports

Case 1.—A girl, aged 12 years, was referred because of persistent headaches and abdominal pain, with failure to gain weight steadily. Her past history was insignificant.

On examination she was of ectomorphic build and 4 ft. 11 in. tall and weighed 67 lb. Her blood-pressure was 110/60 mm. Hg and cardiac impulse normal. A grade I early systolic murmur was present at the apex and along the left parasternal area. A third heart sound was heard at the apex. The remainder of the physical examination was irrelevant. The urine contained albumin, but repeated examinations showed orthostatic albuminuria. A full blood count and the erythrocyte-sedimentation rate were normal. The urine contained no abnormalities on microscopy and was sterile on culture. The blood-urea level was 20 mg. per 100 ml. A chest radiograph (fig. 1) showed a long thin heart which, on deep inspiration, appeared to be lifted off the diaphragm and suspended by the vascular pedicle

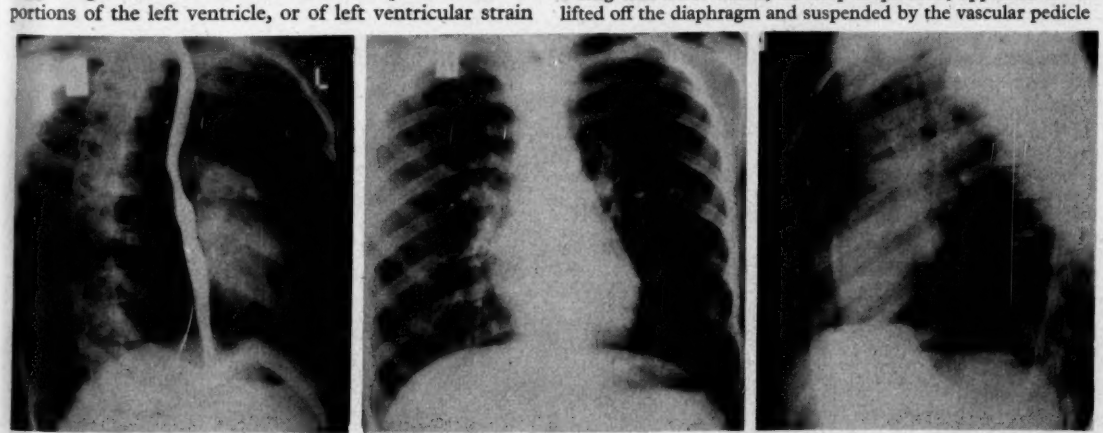

Fig. 1—Teleradiogram of case 1, showing suspended heart: posterior border of inferior vena cava in right anterior oblique view is outlined in white.

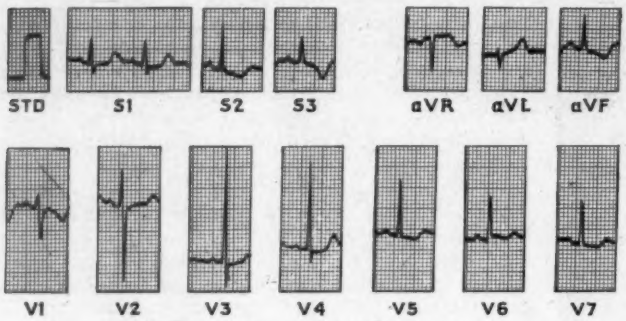

Fig. 2—Electrocardiogram of case 1.

and the inferior vena cava. Electrocardiography showed depressed S-T segments in leads II, III, aVF, V5, V6, and V7, with inverted T waves in III and aVF (fig. 2). V6 recorded one interspace higher showed smaller changes, and the abnormality was diminished but not obliterated by squatting. The tracing was not altered by lying prone or by Valsalva's manœuvre.

Case 2.—A married woman, aged 24, had persistent gnawing pains under her left breast, unrelated to exertion. She often felt breathless, both at rest and on exertion, and she tended to sigh frequently. She was troubled by pins-and-needles in her hands. Her past history was not significant.

On examination she was of mesomorphic build and 5 ft. $6^1/_2$ in. tall and weighed 141 lb. She had congenital ichthyosis of the skin of the trunk and limbs. Her blood-pressure was 120/70 mm. Hg. No abnormalities were detected in her heart or elsewhere. Nothing abnormal was found in her urine. Radiography of her chest (fig. 3) showed a rather globular heart which, in the oblique views, rose high off the diaphragm during inspiration, throwing the inferior vena caval shadow into prominence. Electrocardiography showed inverted T waves in leads II, III, aVF, V4, V5, V6 and CR4 (fig. 4). These changes were less after effort. The picture was not altered by sitting, lying prone, standing, squatting, or the Valsalva manœuvre. Electrocardiography repeated two months later showed no change.

Case 3.—A man, aged 41, had been rejected for military service at the age of 18 because of possible rheumatic heart-disease. In 1936, at the age of 20, he consulted a physician, but no clinical abnormality was found, although the electrocardiogram (fig. 5) showed flattening of the T wave in lead II, and inversion of the T wave in lead III, with pronounced right axis deviation. Since that time he has remained perfectly well and symptom-free. Repeated physical examinations between 1955 and 1957 have shown no cardiac abnormalities. A third heart sound and a grade-I systolic murmur were audible at the apex in 1955, but in 1957 the murmur was absent and the third sound was soft and inconstant. These auscultatory findings were confirmed by phonocardiography.

On examination he had a slightly depressed sternum, but the remainder of the physical examination was normal. He was of mesomorphic build and 5 ft. $7^1/_2$ in. tall and weighed 176 lb. His blood-pressure varied from 130 to 150 systolic and 80 to 90 diastolic. A ballistocardiograph* in 1955 was interpreted as normal. The electrocardiogram (fig. 6), which has remained unchanged since 1955, revealed flattening of the T waves in lead II, with inversion in leads III, aVF, and V6. The degree of right axis deviation was much less than in 1936. The T-wave abnormality disappeared after effort or if the patient was placed in the sitting position with his legs horizontal. Placing the electrode one interspace higher for V6 also produced a normal T wave. The electrocardiogram was not altered by lying prone, standing, or the Valsalva manœuvre. A chest radiograph (fig. 7) showed a heart lifted well off the diaphragm, with prominence of the shadow of the inferior vena cava.

Discussion

If the electrocardiograms discussed by Evans and Lloyd-Thomas (1957) are normal and associated with a peculiar stance of the heart within the thorax, it might be expected that the changes might be found even in children, as in the present case 1. The true incidence of this syndrome in a population cannot be known without mass surveys, but the recognition of the benign nature of the electrocardiographic findings is important, for the sake of reassurance of the patient and for the question of insurance.

Case 2 indicates that the degree of electrocardiographic "abnormality" may be considerable. However, the response to effort, as mentioned by Evans and Lloyd-Thomas (1957), helps to differentiate the changes from those due to coronary-artery disease.

Evans and Lloyd-Thomas (1957) write:

"The separation of the suspended heart from its close contiguity with its surrounding structures, particularly the diaphragm, disturbs the anatomical medium that customarily transmits the varying electrical potential generated by cardiac contraction, and this we consider gives rise to changes associated with this characteristic cardiogram."

If their theory is correct, it is to be expected that, in some cases, posturing of the patient might alter the anatomical relationship of the heart to its environs. In

* Bowen's ballistocardiogram (Smith-Perls model).

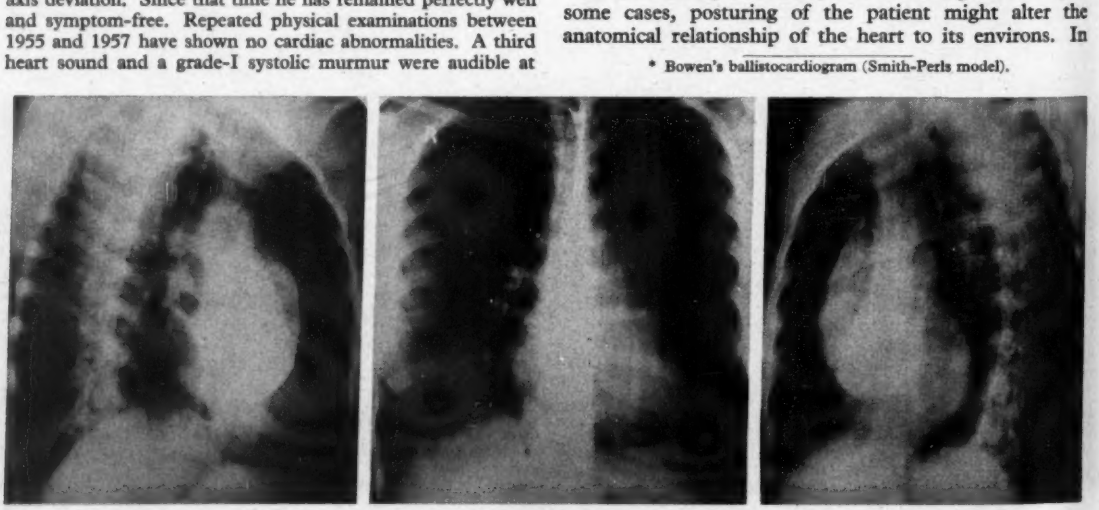

Fig. 3—Teleradiogram of case 2.

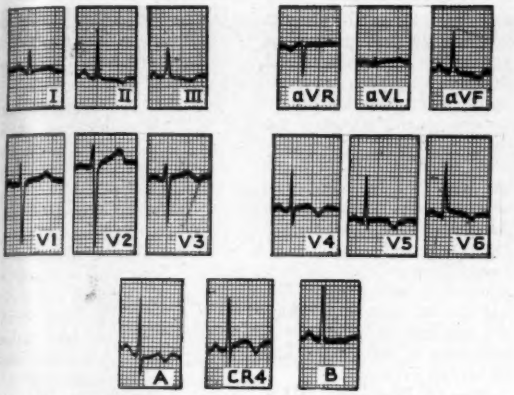

Fig. 4—Electrocardiogram of case 2: A, CR4 recorded after effort; B, lead II recorded after effort.

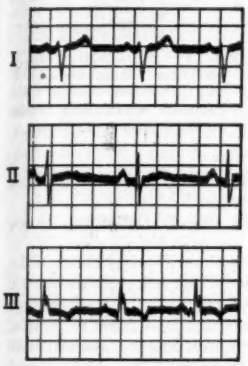

Fig. 5—Electrocardiogram of case 3 in 1936.

case 3, with the patient in the sitting position with his legs horizontal, the T wave, previously inverted, became upright. In case 1 squatting diminished the degree of abnormality.

It therefore seems that the relationship of the heart to its environment, particularly the diaphragm, may be the factor concerned in causing the electrocardiographic "abnormality". Whether this is due to disturbance of the transmission of electrical potential, as stated by Evans and Lloyd-Thomas, or to an alteration of the direction of the repolarisation vector, as seems more probable to us, remains a matter for conjecture. If an electrode could be placed directly on the heart in such a person, the mechanism might be further elucidated.

As Evans and Lloyd-Thomas have done, we also have seen patients with similar radiological appearances of their hearts but with normal electrocardiograms. We have not been able to confirm their observations that closer scrutiny of these radiographs shows more of the heart

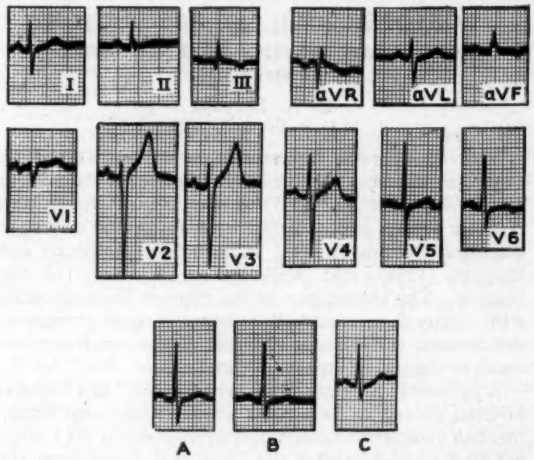

Fig. 6—Electrocardiogram of case 3: A, V6 recorded with patient sitting; B, V6 recorded one intercostal space higher than normal; C, V6 recorded after effort.

shadow in contact with the diaphragm than in those subjects with the "abnormal" electrocardiograms. However, we do not deny the possibility that, in those with normal electrocardiograms, the anatomical relationships of the heart may be different from those of persons with the "abnormal" electrocardiograms discussed above.

Summary and Conclusions

Three further cases of the "syndrome of the suspended heart", as described by Evans and Lloyd-Thomas (1957), are reported, one being in a child aged 12 years. There is an association of a characteristic radiological picture of a heart lifted off the diaphragm and suspended between the vascular pedicle and the inferior vena cava, with an electrocardiogram showing S-T and T changes in posterolateral leads. The benign nature of the syndrome is confirmed, and the abnormal changes are demonstrated in unipolar chest leads, in contrast to the bipolar chest leads used by Evans and Lloyd-Thomas.

We thank Dr. M. M. Suzman for the loan of the electrocardiogram of 1936 in case 3, and Mr. A. M. Shevitz for the reproductions of the radiographs and electrocardiograms.

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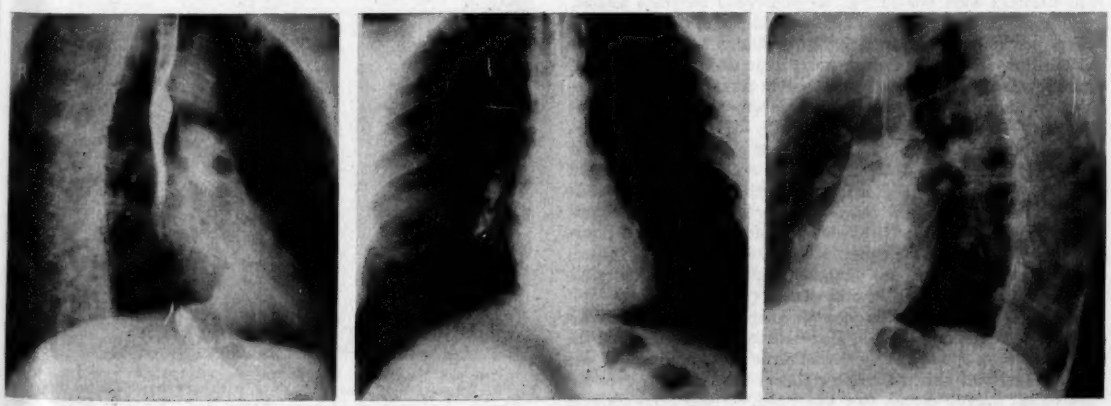

Fig. 7—Teleradiogram of case 3: posterior border of inferior vena cava in right anterior oblique view is outlined in white.

POSTOPERATIVE MALABSORPTION
SECONDARY PROTEIN MALNUTRITION SYNDROME

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M.D. Berlin, L.R.C.P.E.

THE considerable literature on the malabsorption syndrome has been competently reviewed by Adlersberg (1957) and Volwiler (1957) in the United States, and different aspects of postoperative malabsorption have been discussed by Brain (1951, 1953, 1954), Welbourn and Doggart (1956), and Welbourn et al. (1956) in this country. The greater part of the relevant literature deals with steatorrhœa, electrolytes, hæmatological or vitamin deficiencies, and osseous changes. There are few references to the malabsorption of proteins.

A patient with " intractable avitaminosis " in a London hospital proved to have postoperative nutritional failure (protein malnutrition, secondary kwashiorkor). As I could not find a single similar published case I circulated the case-history widely, only to be informed that no such condition has ever been seen in a number of large gastro-enterological departments (Dr. W. I. Card, Dr. F. Avery Jones, Mr. Rodney Smith, and Mr. N. C. Tanner, personal communications). However, scrutinising Mr. Rupert Corbett's postoperative material I found another patient in London who showed repeatedly the fully developed syndrome of protein malnutrition. Publication of these cases may lead to the recognition and study of others.

Case-reports

THE FIRST CASE

This was demonstrated briefly at a meeting of the Nutrition Society last December (Leitner 1958).

A man, aged 61, was admitted to a London Hospital in July, 1953, with four days' history of upper abdominal pain radiating into his left shoulder and arm, vomiting, and severe jaundice. His serum-bilirubin level was 10 mg. per 100 ml., thymol turbidity 2 units, alkaline-phosphatase 120 King-Armstrong units, Hb 13·5 g. per 100 ml., and white cells 22,400 per c.mm. (polymorphs 84%). At operation on Aug. 6, 1953, a hard mass felt in the head of his pancreas was thought to be a carcinoma, but histological examination later showed only chronic pancreatitis. A partial gastrectomy was done, with resection of the head of the pancreas and choledocho-enterostomy with insertion of the pancreatic duct into the duodenum. After operation he temporarily lost weight.

Course of Illness

June, 1955.—He felt ill and was admitted for reassessment. The findings were Hb 12·1 g., all pancreatic enzymes absent, total fæcal fat 36·3 g. per 100 g. of dried fæces, serum-protein 4·7 g. per 100 ml. (albumin 2·5 g., globulin 2·2 g.). A high-protein low-fat diet was given, with large doses of pancreatin, vitamins, and iron, and after four weeks the patient was discharged greatly improved, with serum-protein 5·8 g. per 100 ml.

January, 1956.—Readmitted. He was passing three or four bulky motions daily, had lost weight, and had swelling and ulceration of his legs. The findings were Hb 12·2 g., blood-sugar 102 mg. per 100 ml., serum-proteins 4·3 g., serum-bilirubin 0·9 g., thymol turbidity 4 units, and alkaline phosphatase 18 units. A high-protein low-fat diet was again given, with pancreatin, iron, and vitamins, and three weeks later his condition improved and he was discharged.

May, 1956.—Readmitted complaining of severe pain in his legs and of general malaise; he had œdema of his ankles, punctate pink spots with petechial striæ across his ankles and lower legs, and shallow trophic ulcers scattered all over his body, but mainly on his face and head. It was then thought that he was having neither sufficient nor the right type of care and diet at home. In hospital the purpuric striæ had spread up his legs to his thighs and rump, and a brown pigmentation, which appeared first on his legs, extended towards his trunk. Meanwhile the purpuric staining had involved the whole of his trunk and become more noticeable in the pressure areas. He had no bleeding from his gums. Large doses of vitamins were given orally, and parenterally, but the skin eruption, which was thought to be due to a deficiency of vitamins B and C, further exfoliated.

May 19, 1956.—Hb 11·1 g. per 100 ml., serum-proteins 3·5 g. per 100 ml. (albumin 1·3 g., globulin 2·2 g. per 100 ml.).

May 25, 1956.—Blood-sugar tolerance: fasting 93 mg. per 100 ml., half-hourly figures 119, 150, 190, 193, 170 mg. per 100 ml., with some excretion of sugar shown in the last two specimens.

Fig. 1 — Mosaic-like crazy-pavement dermatosis, with dry wrinkled xerotic skin between lesions and cracks in hyperpigmented areas.

June 21, 1956.—Serum-proteins 3·8 g. (albumin 1·8 g., globulin 2·0 g.).

Aug. 3, 1956.—Serum-proteins 3·6 g. (albumin 1·5 g., globulin 2·1 g.).

Aug. 8, 1956.—Intravenous ascorbic-acid test yielded in the urine only 21 mg. of the expected 200 mg.; blood-pyruvic acid 3·4 mg. per 100 ml. (normal values 0·1–1·0 mg., in marked thiamine deficiency up to 2·0 or 3·0 mg.). 4 pints of plasma, followed by a litre of hydrolysed protein, together with massive doses of vitamin-B complex and vitamin C, was administered subsequently. There was transitory improvement (on Aug. 13 the serum-protein level was 5·2 g.), but the patient relapsed within a week, and new pink spots and striæ and new ulcers appeared.

Aug. 22, 1956.—I saw the patient in consultation at the hospital. He was apathetic, wasted, and obviously ill, with moderate œdema of his ankles and sacrum, and answered questions mechanically. I found no abnormality apart from sluggish tendon-reflexes. Extensive pigmented pellagra-like dermatosis covered the greater part of his body, but places exposed to light were free from such lesions. The skin in

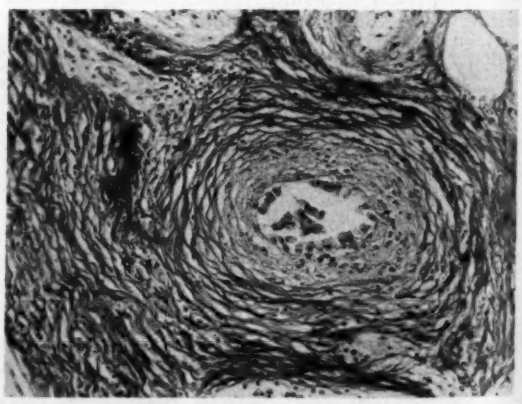

Fig. 2—Dilatation of pancreatic duct, with severe periductal fibrosis, fibrous replacement of parenchyma and complete absence of acinar tissue. (× 130.)

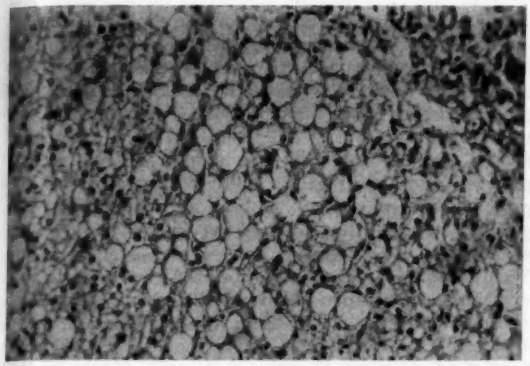

Fig. 3—Very severe fatty change in liver. (× 90.)

between the lesions was dry, wrinkled, and in places scaly and xerotic, with exfoliation, giving the general impression of crazy-pavement or mosaic-like dermatosis. There were numerous cracks, mainly in the hyperpigmented areas (fig. 1). Scattered all over, but mainly on his legs and back, were punctate purpura-like spots and striæ, with pinkish pigmentation, at first sight similar to, but on examination quite different from, the perifollicular hæmorrhages of scurvy. No changes were found in the mucosæ, mucocutaneous junctions, or conjunctivæ. A sample of blood contained carotenoids 5 I.U., vitamin A 56 I.U., and vitamin E 0·14 mg. per 100 ml.

Aug. 29, 1956.—Prothrombin time 20 sec. (normal control 15 sec.); serum-calcium 8·6 mg. per 100 ml.; inorganic phosphorus 4·2 mg. per 100 ml.

Sept. 6, 1956.—Serum-proteins 3·8 g. per 100 ml. (albumin 2·1 g., globulin 1·7 g.). Hb fell to 9·5 g. He died on Sept. 9.

Necropsy

Brain: œdema of white matter; slight atheroma of arteries at base. *Heart:* brown atrophy of myocardium. *Vessels:* slight atheroma of coronary arteries and aorta. *Lungs:* serous pleural effusions, 2 pints. *Peritoneum:* serous ascites 1 pint. *Liver:* very severe fatty change (floats in water); gallbladder distended and lined by smooth grey mucosa; old anastomosis between common bileduct and duodenum, with dilatation of common bileduct. *Stomach:* pyloric portion resected; old gastrojejunal anastomosis (intact); duodenal stump intact; adhesions between loops of upper jejunum in right hypochondrium but no evidence of side-to-side anastomosis. *Pancreas:* head removed; fibrosis of remaining body and tail, with dilatation of pancreatic duct (containing mucus); no communication between pancreatic duct and duodenum. *Spleen:* congested. *Kidneys:* cloudy swelling. *Suprarenals:* atrophied lipoid layer in cortex. *Bone-marrow:* pink hæmopoietic marrow (floats) in neck and upper third of femoral shaft. *Analysis of the liver* showed a fat content of 32·4% and vitamin-A content of 120 I.U. per g. of fixed liver.

Histological Report

Pancreas: hypertrophy of islet tissue, complete atrophy of parenchyma, with chronic inflammation and fibrous replacement, and gross dilatation of duct (fig. 2). Slight chronic inflammation and fibrosis of portal tracts of liver with proliferation of bile canaliculi and extreme fatty change (fig. 3). Chronic inflammation of gastric mucosa. Severe congestion and chronic inflammation of spleen. Congestion, cloudy swelling, and ischæmic changes in *kidney.* Atrophy of *epidermis,* with scattered focal deposits of blood pigment in fibrotic dermis of skin from medial side of left leg. Focal atrophy of voluntary muscle-fibres and endoneural fibrosis of small nerve-bundles in dermis and subcutaneous tissue.

THE SECOND CASE

A married woman, aged 59, was admitted to St. Bartholomew's Hospital on Aug. 31, 1950, having lost 2–3 st. of weight during the preceding year, and developed anorexia, vomiting, and malaise; just before admission she became jaundiced. In hospital a complete duodenal obstruction developed. On Sept. 5 pancreatico-duodenectomy (gastrojejunostomy, cholecystogastrostomy, resection of the head of the pancreas) was performed, and a large neoplasm was removed which completely filled the second part of the duodenum, encircling the common duct and papilla. The growth was of primary duodenal origin, the head of the pancreas and the lymph-nodes not being infiltrated. Recovery was uneventful, and she was discharged on Nov. 1 on pancreatin and iron.

First Readmission (Jan. 28, 1952)

After being well for about a year, she developed steatorrhœa and lost weight in spite of her large appetite. Her face was puffy, and œdema extended almost to both knees. She had dry exfoliative dermatitis, a smooth red tongue, cheilosis, and angular stomatitis. Her serum-protein level was 3·8 g. per 100 ml. (albumin 2·0 g., globulin 1·8 g.). Her fæces contained fat-globules and undigested muscle-fibres. Total fæcal fat 45·1% (10·8% unsplit). Hb 12·4 g. per 100 ml. White cells 4700 per c.mm. (differential count normal). Nitrogen balance negative over four days (5·3 g. of N excreted daily). Of an average daily intake of 46 g. fat (four days) she excreted 26 g. in the stools. She was given protein-rich fat-poor diet with 'Casydrol', 30 g. of proteolised liver extract daily, and vitamin-B complex parenterally. Feb. 22: total proteins 3·8 g. (albumin 1·8 g., globulin 2·0 g.). March 5: total proteins 4·2 g. (albumin and globulin each 2·1 g.); œdema was still present, therefore 100 g. of predigested protein ('Pronutrin') was given daily. March 13: total proteins 5·1 g. (albumin 2·8 g., globulin 2·3 g.). March 28: total proteins 6·7 g. (albumin 3·4 g., globulin 3·3 g.). She was discharged on March 28, 1952, clinically recovered. She had normal formed stools. Her œdema and exfoliative dermatitis had disappeared.

Second Readmission (Jan. 30, 1953)

During the last two months increasing flatulence, anorexia, sweating of her face and neck when eating: "she went to pieces". Pain radiated into her left shoulder and axilla. Puffiness of the face, gross swelling of her legs, considerable sacral œdema, Smooth red denuded tongue in spite of injections of vitamin-B complex by her doctor; bilateral pleural effusion, generalised osteoporosis. Hb 11·8 g., white cells 8000 (differential count normal). Total serum-proteins 3·2 g. (albumin 1·7 g., globulin 1·5 g.). Treatment: high-protein low-fat diet, vitamins, iron, pancreatin, daily infusion of 25 g. of dried serum-albumin in 5% glucose. Feb. 20: total proteins 5·1 g. (albumin 2·8 g., globulin 2·3 g.). Feb. 25: total proteins 5·8 g. (albumin 3·05 g., globulin 2·75 g.); pyruvic-acid-tolerance curve normal (fasting 0·75 mg. of pyruvic acid per 100 ml.; 1·34 mg. per 100 ml. 1 hour after 50 g. of glucose). Feb. 27: discharged feeling well; œdema and pleural effusion had disappeared.

Follow-up

During 1953–57 the patient was regularly followed up by Mr. Corbett with the assistance of Dr. E. F. Scowen. She ate, felt and looked well, and kept her weight steady. Hb on Oct. 5, 1956, was 15·4 g. I examined her with Mr. Corbett on May 24, 1957. Clinically she was well. Total proteins were 6·0 g. (albumin 4·0 g., globulin 2·0 g.), Hb 14·2 g. She reported that every day she ate a meat or a fish meal, usually one or two eggs, and a pint of milk reinforced with casylan. She had taken pancreatin continuously and had intermittent courses of vitamin-B complex. In spite of this she had occasionally a smooth tongue, with mild cheilosis and angular stomatitis.

Third Readmission

On Sept. 18, 1957, she was readmitted under Dr. Scowen. She felt well, apart from sweating of her face after eating, but had become worried about herself. On clinical examination nothing abnormal was found. Investigations showed blood-pressure 135/80 mm. Hg; Hb 14·5 g. per 100 ml.; mean corpuscular volume 84 cμ.; blood-urea 32 mg. per 100 ml.; serum-proteins 5·3 g. per 100 ml. (albumin 3·5 g., globulin 1·8 g.), with normal electrophoretic pattern; thymol turbidity 3 units; total serum-bilirubin 0·5 mg. per 100 ml., direct negative; serum sodium 141, potassium 5, chlorides 111, alkaline reserve 25 mEq. per litre; serum-calcium 8·8 mg. per 100 ml.; inorganic phosphorus 3·7 mg. per 100 ml.; alkaline phosphatase 12 King-Armstrong units. Glucose-tolerance test: fasting 118; half-hourly figures 205, 220, 162, 128, 136, and 118 mg. per 100 ml. Fæces: undigested muscle-fibres and fatty-acid crystals; total fat 30% of the dry matter. Radiography: lungs normal; spine, pelvis, and hands showed diffuse osteoporosis.

Discussion

In case 1 the provisional diagnosis of an intractable vitamin-deficiency state was supported by the symptoms and signs and the biochemical data. My colleague, Dr. T. Moore, commenting on the exceedingly low level of carotenoids and vitamin E, reminded me of his similar findings in kwashiorkor (Trowell et al. 1954a and b). Brock (1955) also has emphasised that the clinical appearances of kwashiorkor may be modified by the complicating deficiencies of vitamins. During the consultation in case 1 the diagnosis of severe avitaminosis was extended to that of nutritional failure, and it soon became evident that the main underlying cause was protein malnutrition. Although, because of the patient's death, further investigations could not be made, the diagnosis was confirmed by the low serum-protein level (3·8 g. per 100 ml. or less) which persisted for several months with inverted albumin/globulin ratio, and subsequently by the necropsy findings. These serum-protein levels, like those in case 2 during the first and second readmissions (3·8 and 3·2 g. per 100 ml. respectively), were substantially lower than those published in large series of kwashiorkor (Dean and Schwartz 1953, Kinnear and Pretorius 1956).

Dermatological lesions are not obligatory signs of protein malnutrition but they do develop in different parts of the world in 25–80% of the cases, and then they always appear on parts of the body not exposed to light. Dryness, scaling, and wrinkling of the skin are always present, often with xerosis and pigmentation, with or without mosaic, crazy-pavement, or enamel-paint-like dermatosis. According to Gopalan (1955) in India it often starts with pinkish punctate discoloration, mainly on the anterolateral aspect of the legs, as in case 1. This has also been observed in Kampala and other places (Trowell et al. 1954a). Although, sometimes a prolongation of the prothrombin-time has been reported in association with these punctate purpura-like spots, neither in case 1 nor in the cases described in Tunis (Caruana et al. 1953) was the prothrombin-time prolonged. In the Tunisian cases the red spots could not be prevented by treatment with vitamin C and vitamin K.

In protein malnutrition the skin lesions always quickly disappear on a high-protein diet, as in case 2 during the first readmission, but neither diet nor plasma infusions had the slightest influence on the exfoliative dermatosis extending over two-thirds of the body's surface in case 1. The serum-protein levels were lower and the clinical symptoms and signs were much more severe in case 2 during the second readmission. In spite of this no dermatological lesions developed as on admission a year earlier.

The protein-malnutrition syndrome is much less common in adults than in children (Trowell et al. 1954a), and the extent and the severity of the skin lesions seem to bear no direct relation to the severity of the disease (Rao 1955). Signs of the syndrome, with typical though limited dermatosis, were described in two Polish refugee women, aged 25 and 40, who suffered great privations during migration through Russia and the Middle East until they reached Uganda (Brown and Trowell 1944), but I am aware only of two other cases of this syndrome ever described in a white man. A Dutch seaman recovered completely on treatment for a year with pancreatin, choline, and a protein-rich diet (Van Steenis 1950). A South African male, aged 40, was dramatically cured after correction of a 6 ft. blind loop surgically constructed 3 ft. proximal to the ileocæcal valve (Krikler and Schrire 1958).

It was impressive how quickly the clinical condition and the serum-protein level reacted in both patients (in case 1 only during the first two readmissions) to simple dietetic measures reinforced by pancreatin and vitamins. Unfortunately we have so far no means of defining protein malnutrition exactly, because we cannot estimate the protein content of the body or assess even approximately the extent of the body's stores of protein. We therefore had to be satisfied with estimating the total serum-proteins, and this, together with the estimation of the protein fractions, seemed to be a surprisingly accurate guide so far as the fluctuation of the clinical condition was concerned. This was recently emphasised also by Waterlow (1956). We found, however, some difficulty in explaining the comparatively sudden fall and sudden rise of serum-protein levels. Both these patients made a spectacular recovery within three to eight weeks with the help of only dietetic measures during their first readmission. Thus the serum-protein level in case 1 rose from 4·7 to 5·8 g. per 100 ml. and in case 2 from 3·8 to 6·7 g. per 100 ml. It therefore appears that the low serum-protein levels were due in both cases to comparatively sudden onset of malabsorption.

Increased fæcal excretion of fat (Gordon-Taylor et al. 1929) and considerable loss of weight (Maclean et al. 1954) have been known for some time to follow gastric operations, even when the secretion of pancreatic enzymes is normal. Resection of the head of the pancreas, on the other hand, leads to excessive loss of both fat and nitrogen in the fæces (Wollaeger et al. 1948, Nicolaysen and Ragaard 1955). Increased excretion of fat and nitrogen in proportion to the pancreatic damage was found also in patients with chronic relapsing pancreatitis (Dornberger et al. 1948). Pancreatic enzymes were absent in case 1, but this did not prevent a rise in the serum-protein level within a few weeks from 4·7 to 5·8 g. per 100 ml. Although at times high-protein diet and intravenous infusion of comparatively small amounts of albumin seemed to restore quickly the malabsorption defect (second readmission of case 2), at other times large parenteral infusions of plasma yielded at best an improvement for only a few days, followed by death (case 1, third readmission).

During the siege of Budapest Véghelyi (1948) noticed that babies fed on a diet poor in animal proteins developed gross œdema and severe fatty infiltration of the liver following decrease in pancreatic secretion. The development of pancreatic failure took only one or two weeks; the younger the child the quicker was the failure. The whole process could be reversed within a few days if enough milk or methionine was given. It was much harder to reverse, or became irreversible, if treatment started later in the illness. The macroscopic appearance of the pancreas was in these cases almost normal, but microscopy showed small shrunken acinar cells, with depletion of the cytoplasm and disappearance of the zymogen granules, fibrosis, and scarring. By experimental feeding similar changes were produced in rats, and the excretory changes in the pancreas preceded fatty infiltration of the liver. Davies (1948) described the atrophy of the acinar cells in the pancreas, with a diminution in the numbers of secretory granules, gross fibrosis, and dilatation of the ducts, as the fundamental lesion in kwashiorkor, which was necessarily followed by extensive fatty infiltration of the liver. " In a man of 24 the pancreas had been almost completely superseded by fibrous tissue ", a description very similar to our case 1.

Friedman and Friedman (1946), by giving a protein-poor diet to rats, produced a loss of cytoplasm in the acinar cells of the pancreas until only a thin rim remained round the vesicular nucleus. Fatty infiltration of the liver was present in all the rats. Similar changes were produced by giving ethionine (an antagonist of methionine); the lesions could be prevented by previous administration of methionine but not cystein or

glucose, both of which usually prevent fatty infiltration of the liver (Farber and Popper 1950). Moreover the pancreas produces more enzymes on a diet high in complete proteins (containing all essential aminoacids) than on a diet that is either low in proteins or does not contain complete proteins—e.g., gelatin and zein (Magee and Anderson 1955).

From these experiments it appears that the normal structure and function of the pancreas depend greatly on an adequate supply of complete proteins. The experiments are also in agreement with the clinical, experimental, and pathological work of Davies (1948) and Véghelyi (1948) and with newer findings that severe atrophy of the acinar cells, with fibrosis of the pancreas of whatever ætiology, produces necessarily an extensive fatty infiltration of the liver (Bras et al. 1956). Furthermore Véghelyi et al. (1950) have shown that, in early cases, an adequate supply of proteins was followed within ten days by clinical improvement and by a rise in the serum-protein level; improvement, if any, in more chronic cases took much longer. This observation is borne out by my own experiences: both patients reported here improved quickly after being given a high-protein diet during their first readmission. The serum-protein level in case 2 rose during the second readmission from 3·2 to 5·8 g. per 100 ml. within three weeks on a high-protein diet and intravenous dried serum-albumin 25 g. daily, and coincidentally the gross generalised œdema and bilateral pleural effusion disappeared completely, and no further relapse occurred during the subsequent five years. In case 1, however, where the readmissions occurred only at a more severe stage of the disease, recovery was impossible.

In the two cases here recorded this postoperative malabsorption state led to the typical syndrome of secondary protein malnutrition. All the evidence suggests that the pancreas, the organ with the greatest protein turnover in the body, has a key position in the development of the protein-malnutrition syndrome. It appears that the vicious circle leading to the more severe stages of protein malnutrition and eventually to death might be arrested nearly at any stage—e.g., fatty infiltration of the liver, and partial pancreatic fibrosis—provided that structural changes are still reversible; but, when extensive shrinking of the acinar tissue, with gross atrophy of the parenchyma of the pancreas and massive fibrous replacement and scarring, has taken place, interrupting communication between pancreas and duodenum, as in case 1, no reversion is possible.

Summary

Two patients are reported who developed a syndrome of protein malnutrition, hitherto undescribed, some years after pancreaticoduodenectomy.

The possible mechanism of the malabsorption leading to secondary protein malnutrition is discussed.

My thanks are due to Dr. T. St. M. Norris and Mr. Rupert Corbett for asking me to see cases 1 and 2 respectively, for much advice, and for permission to publish; to Dr. T. Moore, Dr. I. M. Sharman, and Dr. E. Montuschi for their help; and to many colleagues in this country and overseas who discussed several aspects of protein malnutrition with me, particularly Prof. J. F. Brock, Prof. J. N. P. Davies, Prof. Kenneth Hill, and Prof. B. S. Platt, and Dr. W. I. Card, Dr. H. C. Trowell, Dr. J. C. Waterlow, and Dr. Cicely Williams.

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"FALSE" SICKLE CELLS
UNDER THE POLARISING MICROSCOPE

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SICKLE-CELL trait and sickle-cell anæmia can be distinguished from one another by examining fresh preparations of the venous blood under anaerobic conditions (Sherman 1940). In persons with the trait less than 1% of the erythrocytes are sickled, whereas in sickle-cell anæmia the proportion is 30–60%.

During research in the Petromagoula area, where sickle-cell anæmia and trait are prevalent (Choremis et al. 1953, 1957), 37 members of the families of 12 patients were found to have the trait. In fresh preparations of their venous blood, with added sodium metabisulphite, sickle cells appeared after six to twelve hours' incubation, a holly-leaf form being predominant (fig. 1).

Silvestroni and Bianco (1946) in Italy, noted differences in the sickling between patients and carriers of the trait. In the carriers the sickling took longer to appear (sometimes twenty to twenty-four hours). Only a small proportion of the cells assumed the holly-leaf form.

Sturgeon et al. (1955) described in sickle-cell-D disease a slow and limited sickling, with holly-leaf forms predominant, whereas in sickle-cell anæmia sickling was rapid and complete.

In 1952 we observed in healthy persons a slow sickling limited to a small proportion of red cells, but this was subsequently held to be false (Caminopetros 1952, Choremis et al. 1953, Lie-Injo Luan Eng 1953). Our sickle cells were ascribed to external stresses—notably, long incubation. In general, sickling of cells after more than twelve hours' incubation, even where it is complete, is taken as false. Thus, in the Kakwa tribe the sickle-cell incidence rose from 12% to 25% when the preparations were left overnight (Lehmann and Raper 1949), and this increase was attributed to the appearance of false sickle cells. On the other hand it is difficult to see why

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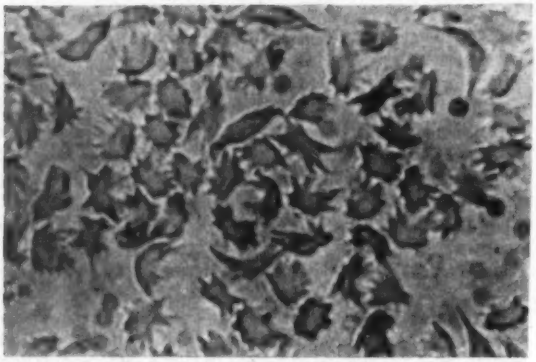

Fig. 1—Sickle-cell trait. Moderate sickling. Predominance of holly-leaf forms. (×550.)

"false" sickling has so far been observed only in peoples who exhibit the trait, and not in the blood of Europeans, in whom it is absent.

Since 1952 we have seen 106 new cases of the limited form of sickling (fig. 2). Of the people showing it, some come from the Greek mainland or islands, while others are Greek and Armenian refugees from Asia Minor or gipsy settlers in Greece. Some of them—not always related to patients with anæmia—have signs of the trait such as target cells, and increased resistance of red cells. Nevertheless it was still necessary to prove the existence of S hæmoglobin in these cases, since this is thought to be the agent responsible for sickling (Pauling et al. 1949).

The characteristic optical property of S hæmoglobin, either in sickle-cells or in its solutions is birefringence, and this is seen under the polarising microscope (Sherman 1940, Perutz and Mitchison 1950, Ascenzi and Silvestroni 1953). We decided to ascertain whether the so-called false sickle-cells were birefringent.

Our examinations were made at the Institute of Geology with a 'Panphot' Ernst Leitz polarising microscope. Its arc lamp provided the necessary high-intensity light. The choice of objective (P6L 45 : 1) and eyepiece 12x were satisfactory.

Blood from 73 of our 106 cases with slow and limited sickling was examined, on the first or second day of the appearance of sickle-cells. Unlike the red cells of normal discoid form, all these cells exhibited definite birefringence (fig. 3).

These findings point to the presence of S hæmoglobin. Hence the sickling in these cases, though restricted and incomplete, must be due to intrinsic factors. It is not an artefact.

We now think it probable that sickle-cell anæmia is caused by multiple genetic factors, and that the complete form of sickling may decline to minor forms, and eventually be extinguished.

It is well established that in the sickle-cell trait the amount of S hæmoglobin ranges from 22% to 46%. An exceptional case has been reported in which it was 5%, but the red cells could not be sickled. The amount of S hæmoglobin in cases with slow and limited sickling will have to be determined. We may note, however, that the abnormality of the red cells is not confined to the hæmoglobin but extends to the cytoplasm and the cell membrane (Perutz and Mitchison 1950, Ponder 1951).

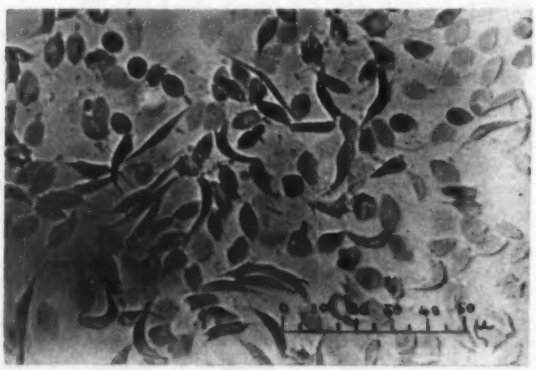

Fig. 2—Slow and limited sickling after 8 hours' incubation.

Summary

In 73 cases showing the slow and limited sickling which was described in 1952 the sickled red cells have been examined under a polarising microscope. They were found to be birefringent, as in cases of complete sickling.

This finding supports the view that the sickling observed, though slow and limited, is genuine—not false, as has been suggested.

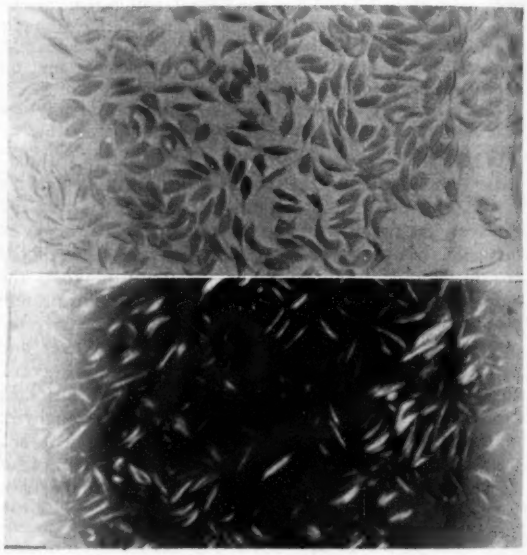

Fig. 3—Lowest degree of sickling. *Above:* Under ordinary microscope. *Below:* the same fresh preparation under polarising microscope, showing intense birefringence.

We are indebted to Mr. D. Frangomanolaki for his help in the microscopical examinations; to Mr. C. Zachos, director of the Institute of Geology and Subsurface Research; and to Mr. G. Marinos, chief of service of the institute.

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New Inventions

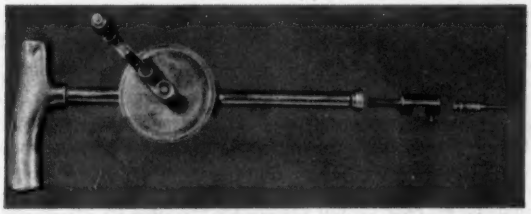
A NEEDLE TREPHINE

FOR the past three years I have used a needle trephine which can be readily made in any laboratory. The trephine has been used both manually and with electrical power. It has been employed in man and laboratory animals for placing surface electrodes, and deep cortical electrodes, emergent exploration of the subdural space and subarachnoid space, placing needle electrodes in the deep nuclei of the brain, and tapping the ventricular system for placing air and phenolsulphonphthalein solution for evaluation of the ventricular system.

The trephine is made by taking a 16-gauge lumbar-puncture needle, and filing a groove in the hilt of the needle 90° from the original groove that receives the locking tongue of the stylet. The stylet is then rotated 90° from its normal position and set into the prepared groove. The needle with the stylet in place is then sawed at 45° angle 2 cm. from where the hilt begins. The opposite side of the needle and stylet are filed to a 45° angle from the horizontal. Once this is done, the stylet is rotated again back to its normal, originally designed position which makes for a point with opposing 45° angles resulting in serrated or cutting edges.

A small adapter was made out of brass which receives the hilt of the needle and is locked into place by a set screw. The opposite end of the adapter has a straight shaft which can be fitted into a Jacob's chuck or into a locking twist drill chuck (see figure).

The obvious advantage of this needle trephine is that it perforates the skull without a surgical incision. With the stylet of the needle trephine in its normal position, the scalp is perforated under local anæsthesia as a puncture. Once the outer table of the skull is encountered, the stylet of the needle is turned into its cutting position of 180°, and the hilt of the needle is placed into the adapted chuck. With a limited number of turns, the needle passes through the tables and the needle



Twist drill, chuck adapter, and needle trephine.

can be felt making its final break through the inner table. The length of the needle precludes it going more than a few millimetres beyond the inner table. If the needle trephine has been directed properly for the intended target, the smaller needle or the needle electrode can be taken and advanced through the trephine needle. In the case of a ventriculogram, a no. 20 smooth bevelled needle can be directed into the lateral ventricle. If the line of flight of the needle trephine has not been properly directed, it is necessary to remove the needle trephine and to advance the smaller ventricular cannula or the smaller electrode needle in the proper direction, which is possible because these needles are small compared to the trephine needle, and their direction can be changed. The puncture opening in the scalp is readily sealed with 'Aeroplast'.

The needle trephine has all the disadvantages of the twist drill holes; but these disadvantages are outweighed by the simplicity when it is not desirable to display the brain surface. I have not employed this drill in tumour biopsy, or to tap cerebral or suprasella cysts, but the instrument would lend itself well to these procedures. With it I have placed over 100 trephine openings over various areas of the skull. There has been no infection or hæmorrhage. The procedure is not unduly painful to the patient.

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Reviews of Books

Attempted Suicide

Its Social Significance and Effects. E. STENGEL, M.D., M.R.C.P., professor of psychiatry, University of Sheffield; NANCY G. COOK, A.M.I.A., psychiatric social worker. Maudsley Monographs no. 4. London: Chapman & Hall, for the Institute of Psychiatry. 1958. Pp. 136. 25*s*.

SUICIDE is a subject of great psychiatric and sociological importance with many unsolved and even unexamined problems. In 1952 Professor Stengel first pointed out that the environmental setting of attempted suicide and its repercussions on society had never been adequately investigated, partly because it was assumed that successful and unsuccessful suicides formed a homogeneous group. He propounded a number of questions for future research, some results of which were summarised in 1956 and are presented in detail here. He and his collaborators have studied "the relation of the individual to the social environment in the course of the suicidal attempt", its "effects . . . on the person's social relationships", and "the reactions of the human environment and of society" in five groups totalling 630 patients admitted to hospital (three groups in observation wards, one in a psychiatric hospital, and one in a general hospital) and compared them with a series of suicides from a coroner's court. Two of the groups followed up for as long as six years confirmed the clinical impression that only a minority finally succumbed to suicide. They conclude that attempted and successful suicides should be regarded "as two different though overlapping populations". In contrast to suicide, "suicidal acts . . . irrespective of psychiatric background" are "incidents in the course of struggle for adjustment . . . social behaviour patterns" not "self-destructive" but "an alarm signal" or "appeal to the human environment".

This thesis is probably correct for a proportion of cases but applied to all seems an oversimplification on the authors' own evidence. It does not explain the steep rise of suicidal attempts in the last decade—partly due to the easy availability of sedative drugs for minor psychiatric disturbances—at a time when social conditions and community care have steadily improved. Nor can it explain suicidal attempts in response to hallucinations, delusions, the conviction of severe illness, fear of insanity, and insomnia, or following crimes of violence or suicide pacts, or in patients already living a sheltered community life, as in mental hospitals.

The book makes difficult reading, partly because of its style. The text is broken by 33 tables, not all helpful or readily comprehensible. 44 representative case-histories, varying in length from 4 lines to almost a page, demonstrate that to obtain and present sound psychiatric case material is the chief difficulty in studies based on large numbers of patients.

The Art of Clinical Refraction

T. H. WHITTINGTON, M.D., M.R.C.P., D.O.M.S., ophthalmic physician, the Royal Eye Hospital, London. London: Oxford University Press. 1958. Pp. 294. 30*s*.

Dr. Whittington has succeeded in animating refractive work, and his readers will be stimulated by his zest and interesting presentation of clinical problems in a subject too often considered dull and dry. Although refraction is a small part of ophthalmology it is a large part of routine practice for most ophthalmologists. An intelligent appreciation of all the factors concerned in a patient's visual discomfort, and a conscientious application of the necessary subjective and objective tests, are essential for the relief of symptoms and reassurance of the patient.

The book is practical and devoid of higher mathematics, and its value lies in the physician's approach to the art as well as

the science of refraction. Criticism concerns trifling errors. Fig. 57 (*a*) and (*b*), to illustrate the actions of the superior and inferior oblique muscles, are incorrectly drawn to meet the description in the text, and fig. 54 (the Maddox rod test) would look better if all the vertical test results were set out in one row and the horizontal in the other. " Spasmodic " is perhaps an inappropriate description for contractural torticollis (wry neck) of orthopædic interest.

The author has put into the book much wisdom, the outcome of long clinical experience, enriched by the human interest he has taken in his patients. It will therefore be of particular value to the young ophthalmologist—and indeed to many of maturer years.

Enzymes

MALCOLM DIXON, SC.D., F.R.S., reader in enzyme biochemistry in the University of Cambridge, fellow of King's College, Cambridge; EDWIN C. WEBB, M.A., PH.D., lecturer in biochemistry in the University of Cambridge. London: Longmans, Green. New York: Academic Press. 1958. Pp. 782. 90*s*.

THIS is a scholarly and original book involving much of the authors' highly personal and critical approach to enzyme problems in addition to a comprehensive survey of the literature of known enzymes. The subject is treated at a level suitable for research-workers and advanced students. The book is mainly concerned with the elucidation of general principles underlying the nature, structure, mechanism of action, and kinetics of enzymes, and is only secondarily an account of the more functional aspects of the role of enzymes in metabolism. In order to clear the ground for the very full treatment of basic principles, factual data concerning individual enzymes, including details of sources, substrates attacked, activators, and the chemical reactions catalysed, have been grouped together in encyclopædic tables. Thus table v is a list of 659 enzymes occupying 42 pages arranged according to the reaction-type and thought to include, with literature references, all clearly identified enzymes described up to 1957. The classification follows that already brilliantly sketched in 1949 in Dr. Dixon's small book *Multi-enzyme Systems*. A valuable step forward in enzyme classification has undoubtedly been achieved. This book is a highly valuable contribution to knowledge of and should become a standard work on the basic principles of enzymology.

Laboratory Medicine: Hematology

JOHN B. MIALE, M.D., professor of pathology, University of Miami School of Medicine, director of clinical pathology, Jackson Memorial Hospital, Miami, Florida. London: Henry Kimpton. 1958. Pp. 735. 112*s*. 6*d*.

THIS is not a book for physicians, as the title is understood in this country, but for clinical pathologists, and really for those specialising in hæmatology. The general clinical pathologist may find it useful as a reference book, for it is detailed, up-to-the-minute, and surprisingly complete. But the effort to make it complete has involved the author in masses of detail that do not make easy reading or allow him to give clear indications for action. Much of the information is helpfully gathered into tables, but, in a manner often seen in American texts, they give no indication about relative importance. Thus, table 22 lists 34 chemicals that have caused methæmoglobinæmia, together with 6 other causes, including " ingestion of coloured wax crayons or chalk "; table 67 lists 55 causes of eosinophilia—a remarkable feat, though few of the causes are important in practice. A more valuable section lists 37 cases of interpretation of bone-marrow findings, giving brief details of the history, physical examination, and other pertinent laboratory findings together with a discussion of how all this material was put together in reaching a diagnosis. This is indeed the stuff of medicine, but this method is not used in other sections. It is hard to find any point in hæmatology that is not mentioned: for example, the book includes the changes in the differential white-cell count from birth to 21 years; the laboratory findings in the hæmoglobinopathies, including Hb-I trait; and the recommended types of blood or blood product for transfusion in blood diseases.

The bibliography is immense and all titles are given of papers listed. The illustrations are mostly black-and-white, but some are from colour photomicrographs; the reproduction of the colour photographs is not very good; Professor Miale knows well the diagnostic importance of clear nuclear detail in erythroblasts, but the pictures of pronormoblast and other normoblasts show featureless magenta blobs for nuclei. The book will find its most popular use among the reference works in the clinical laboratory.

Ulcerative Colitis

HARRY E. BACON, B.S., M.D., SC.D., LL.D., F.A.C.S., F.A.P.S., professor and head of department of proctology, Temple University, Philadelphia. Philadelphia: J. B. Lippincott. London: Pitman Medical Publishing Co. 1958. Pp. 395. 120*s*.

Dr. Bacon is well known to British proctologists not only through his many writings but as a man of thoroughness and energy. A book from him, therefore, on the topical subject of ulcerative colitis is welcome—all the more so because only two other works are solely devoted to this subject. This latest one is essentially factual in its approach and has the virtue of being comprehensive with but few omissions of reference to relevant work. The ætiological hypotheses are presented fairly. Surgical detail is contained only in the last half of the work; and earlier chapters contain much useful information, ranging from pathology, diagnosis, and complications to conservative therapy, including the use of steroids. Appropriately a chapter on the effect of the disease on pregnancy and vice versa is included. The book is illustrated profusely, and sometimes superfluously —a pity, since the cost is high for a work on a subject with limited appeal.

External Collimation Detection of Intracranial Neoplasia with Unstable Nuclides

G. M. SHY, M.D., M.R.C.P., R. B. BRADLEY, B.S., W. B. MATTHEWS, Jr., B.S., department of health, education and welfare, Bethesda, U.S.A. Edinburgh and London: E. & S. Livingstone. 1958. Pp. 144. 30*s*.

THE title of this book reflects fairly its highly technical content and style of expression. Injections into either the arteries leading to the brain or the cerebrospinal space to confirm the diagnosis of a cerebral tumour cause discomfort to the patient and carry certain hazards. The development of alternative methods for detecting and localising tumours within the skull is clearly important. The authors recount their experience in using radioactive isotopes, which may be concentrated in neoplastic tissue. The position of the tumour may be determined by the use of external counters with little disturbance to the patient. The work described here is an advance in a difficult field; but it might perhaps have been more suitably published in shorter form, in plainer English, in a specialised journal.

The Excitable Cortex in Conscious Man (London: Liverpool University Press. 1958. Pp. 43. 10*s*. 6*d*.).—This little book, which is a transcript of Dr. Wilder Penfield's Sherrington lecture, gives a brief survey of some of his work, with various colleagues, on the response to electrical stimulation of the human cerebral cortex exposed after craniotomy under local anæsthesia. The information obtained in this way is, as Dr. Penfield is careful to emphasise, a by-product of surgical procedures undertaken with a definite therapeutic end in view. Two cases of epilepsy in which elaborate psychical phenomena were elicited are described in some detail; but much of the book is devoted to an account in general terms of the properties of the cortical regions revealed by electrical stimulation and to schemata illustrating the author's interpretation of these properties. If at times the argument seems a little facile, it must be allowed that in a necessarily abbreviated and primarily vivavoce presentation some elision is scarcely avoidable. The book can be recommended not only as a convenient up-to-date summary of, but also a readily assimilable introduction to, the fascinating work done in the author's clinic.

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More New Steroids

THE synthesis of new steroids, measurement of their effect in animals, and submission of selected examples to clinical trial are proceeding with increasing momentum. Modifications of the cortisone or hydrocortisone molecule which have yielded substances of therapeutic interest have included the insertion of a double bond in ring A, a halogen atom at C19, and a hydroxyl or methyl group in the α configuration at C16. Singly or in combination these changes have produced substances of widely different character. Fludrocortisone, the 9-α-fluoro- derivative of hydrocortisone,[1] is a much more potent "anti-inflammatory" agent than its parent steroid but is limited in its clinical applications by an even greater enhancement of sodium-retaining activity. The unsaturated derivatives of cortisone and hydrocortisone, the δ or "predni" steroids—prednisone and prednisolone—are also more active anti-inflammatory agents than their precursors but have very little mineralocorticoid activity except in very large doses. In addition to topical application 9-α-fluoro-hydrocortisone has a place in the treatment of some cases of Addison's disease and after adrenalectomy. The δ steroids have largely replaced cortisone in the treatment of diseases such as rheumatoid arthritis and asthma; their weak mineralocorticoid activity is an asset, and in rheumatoid arthritis they promise to maintain control beyond the time when the effect of cortisone begins to wane.

At the International Congress on Rheumatic Diseases last year the effects of a still newer steroid, triamcinolone, were discussed by FREYBERG et al.[2] This substance, prepared by BERNSTEIN et al.,[3] is hydrocortisone modified by a double bond in ring A, a fluorine atom at C9, and a hydroxyl group at C16. The last of these modifications converts a powerful mineralocorticoid into a substance with a sodium-diuretic action; its anti-inflammatory activity is slightly greater than that of prednisone or prednisolone. Clinicians are unlikely to be impressed by the ability of a 4 mg. tablet of triamcinolone to do the same good work as a 5 mg. tablet of prednisolone unless the former has other advantages. From several reports it is obvious that triamcinolone has some side-effects not shared with other steroids; among these FREYBERG et al.[2] mentioned severe headache, dizziness, anorexia, nausea, fatigue, and progressive loss of weight; but peptic ulceration did not occur. In our columns this week Dr. DUDLEY HART and his colleagues report a comparison between the effects of prednisolone and triamcinolone in rheumatoid arthritis. At a 4 : 5 dose ratio of triamcinolone to prednisolone the former was slightly more effective. Dyspepsia often persisted when triamcinolone was substituted for prednisolone, but no final conclusion was reached about the comparative risk of peptic ulceration. SHELLEY et al.[4] have reported that triamcinolone is effective in psoriasis—a disease which responds poorly if at all to other steroids. Of 31 patients with systemic lupus erythematosus treated by DUBOIS[5] with triamcinolone, only 1 developed a new peptic ulcer, and a pre-existing ulcer healed during treatment with the steroid. HART et al. did not observe any of the unusual side-effects of triamcinolone except postprandial flushing. Some of DUBOIS' patients, treated with much higher doses, developed profound weakness of muscles —particularly the extensors of the legs and the deep muscles of the back. This disturbing effect was limited to women and slowly disappeared when prednisone or hydrocortisone was given instead of triamcinolone. Furthermore many patients gradually lost weight—only partly from loss of fluid—and hirsutism and striæ were more prominent than in patients treated with other steroids. The men in this series showed no "cushingoid" features, and for this reason DUBOIS believes that triamcinolone may be the steroid of choice in men. Of these patients with systemic lupus erythematosus most felt better during treatment with triamcinolone than with other steroids. A hitherto unreported and unexpected effect of triamcinolone is described on another page by Dr. WELLS. 3 patients treated with the steroid—1 for thrombocytopenic purpura and 2 for asthma—developed pains in their joints. In 2 of these patients the appearance of the joints mimicked rheumatoid arthritis; in all 3 the arthropathy disappeared when prednisolone was substituted for triamcinolone. It is conceivable that the patient with thrombocytopenic purpura had lupus erythematosus and that the joint symptoms were part of this disease; it is hard to explain their appearance during treatment with triamcinolone (but not with prednisolone) and equally difficult to explain the similar sequence in the patients with asthma. The balance of evidence seems to suggest that arthropathy was a direct effect of the treatment. Clearly much more must be learnt about the advantages and disadvantages of triamcinolone. It may at times be rather more effective than the δ steroids; it may (by virtue of its diuretic activity) be useful in patients with cardiac decompensation, and in those who gain weight rapidly, or whose blood-pressure rises, when treated with other steroids. It shows considerable promise in psoriasis. Further evidence is needed about the risk of peptic ulcer or osteoporosis—major bugbears of steroid therapy—although it has been claimed that it is less likely to provoke these effects than other steroids. The muscular weakness described by DUBOIS may be troublesome only when high doses have to be used. The unexpected effect in WELLS' patients will clearly repay close study.

Yet another new steroid has been brought into clinical use. This has the same structure as triamcinolone

1. Fried, J. *Ann. N.Y. Acad. Sci.* 1955, **61**, 573.
2. Freyberg, R. H., Bernsten, C. A., Jr., Hellman, L., Gallagher, T. F. Paper read to 9th International Congress on Rheumatic Diseases, Toronto, 1957.
3. Bernstein, S., Lenhard, R. H., Allen, W. S., Heller, M., Littell, R., Stolar, S. M., Feldman, L. I., Blank, H. H. *J. Amer. chem. Soc.* 1956, **78**, 5693.
4. Shelley, W. B., Harun, J. S., Pillsbury, D. M. *J. Amer. med. Ass.* 1958, **167**, 959.
5. Dubois, E. L. *ibid.* p. 1590.

except that a methyl instead of a hydroxyl group occupies the 16α carbon position. This substance, hexadecadrol (' Decadron '), synthesised in the laboratories of Merck, Sharp & Dohme, was used by BOLAND [6] in 21 cases of rheumatoid arthritis. It proved to be 5–10 times as potent as prednisolone in controlling the disease; significant gastrointestinal symptoms did not develop, but the trial was preliminary and too brief for judgment of side-effects. In animals the anti-inflammatory effect was 190 times that of hydrocortisone, but the glycogenic activity was enhanced by a factor of only 17. Sodium retention was not demonstrable in adrenalectomised rats. The dissociation of anti-inflammatory and glycogenic activity, which are so closely related in other steroids, is striking, and reports on the long-term clinical use of this steroid will be awaited with interest.

In assessing these products of the ingenuity of steroid chemists, potency is important only as a factor in the therapeutic ratio. Dissociation of desirable from undesirable effects would be a great step forward.

Thymectomy and Myasthenia Gravis

THE association between abnormalities of the thymus and myasthenia gravis was recognised over half a century ago. In most series of myasthenics rather more than a tenth have radiologically demonstrable enlargement of the thymus, and hyperplasia has been observed in over half the myasthenic thymuses examined histologically. Nevertheless the precise relation between the thymus and myasthenia remains something of a mystery; for, although it would be easy to assume that the thymus produces a curare-like substance which interferes with neuromuscular transmission, it may be that an independent process, as yet unidentified, results simultaneously in the myasthenic state and enlargement or hyperplasia of the thymus. The hyperplastic thymus may then in its turn accentuate and perpetuate the myasthenic muscular response. The notion that myasthenia is accompanied by structural changes at the motor end-plate and is not necessarily due to some hypothetical thymic secretion is now receiving the attention it undoubtedly deserves; and we hope that the lead given by WOOLF et al.[7] proves profitable. WILSON et al.[8] showed that the myasthenic thymus has a high neuromuscular-blocking activity, and also that the greater the benefit of thymectomy in a given case the greater had been the blocking activity of that particular thymus. On the other hand the thymus of children and of an adult who was certainly not myasthenic (this specimen was obtained at necropsy) also exhibited a high blocking activity. Furthermore extracts of thymus from undoubted cases of myasthenia exhibited no high blocking activity. In other words the link is not so obvious or so direct as some workers would have us believe. The simple notion of thymic secretion fails to take into account the curiously selective affection of the ocular or bulbar muscles noted particularly by GROB [9] and by FERGUSON et al.,[10] and also seems difficult to reconcile with the fact that exercise of one part of the body may aggravate the myasthenic response in another.[11]

Because of the conflicting physiological and pharmacological evidence we must turn to the evidence from clinical studies. Is it in fact certain that surgical removal or radiotherapeutic destruction of the thymus is followed by significant improvement in myasthenia? Since BLALOCK [12] in 1939 reintroduced this operation, workers at various centres have considered the statistical evidence in the most careful and painstaking way. In 1954 we concluded [13] that "until criteria for selection are improved, thymectomy will not commend itself for patients well maintained under medical management, those with localised ocular myasthenia, those in the older age-groups, or those with longstanding symptoms. The choice of treatment remains most difficult in the young myasthenic with generalised symptoms and a short history. KEYNES's good results will influence some physicians in their choice, while the findings at the Johns Hopkins Hospital and the Mayo Clinic will make others hesitate". The allusion to Johns Hopkins related to the work of GROB,[9] who had concluded that there was no striking difference between the results of thymectomy and those of medical management; the Mayo Clinic workers were EATON and CLAGETT,[14] who in 1950 had also found no significant statistical difference. These two workers have since revised their opinion.[15] Their initial conclusion that thymectomy had no significant beneficial effect seems to have sprung from their not at that time considering thymic tumours in a separate group. Recent surveys have shown that in patients with such tumours the mortality is apparently not lowered by operation, which, however, may improve the myasthenic state for a time. It seems possible that the best treatment in these cases may prove to be radiotherapy, for the postoperative death-rate is not inconsiderable. KEYNES [16] recommended surgery in these thymomatous cases only after radiotherapy had been applied, but alluded to three patients who remained well after radiotherapy without operation. It is perhaps surprising that a tumour in the thymus should render removal of that organ less beneficial than in cases where there is no tumour; but this is in keeping with the generally paradoxical role of the thymus in myasthenia.

SIMPSON [17] has now reviewed 404 cases of myasthenia comprising those seen at the National Hospital for Nervous Diseases together with those dealt with by KEYNES in his extensive series of thymectomies. SIMPSON was able to trace 374 of these 404 patients, and 245 of the 374 had survived. Of these 245, 181

6. Boland, E. W. *Calif. Med.* 1958, **88**, 417.
7. Woolf, A. L., Bagnall, H. J., Bauwens, P., Bickerstaff, E. R. *J. Path. Bact.* 1956, **61**, 173.
8. Wilson, A., Obrist, O. R., Wilson, H. *Lancet*, 1953, ii, 368.
9. Grob, D. *J. Amer. med. Ass.* 1953, **153**, 529.
10. Ferguson, F. R., Hutchinson, E. C., Liversedge, L. A. *Lancet*, 1955, ii, 636.
11. Wilson, A., Stoner, H. B. *Quart. J. Med.* 1944, **13**, 1.
12. Blalock, A., Mason, M. F., Morgan, H. J., Riven, S. S. *Ann. Surg.* 1939, **110**, 544.
13. *Lancet*, 1954, i, 352.
14. Eaton, L. M., Clagett, O. T. *J. Amer. med. Ass.* 1950, **142**, 963.
15. Eaton, L. M., Clagett, O. T. *Amer. J. Med.* 1955, **18**, 703.
16. Keynes, G. *Lancet*, 1954, i, 1197.
17. Simpson, J. A. *Brain*, 1958, **81**, 112.

were re-examined, and the remainder completed a detailed questionary. The total series comprised 294 patients who had undergone thymectomy and 110 who had not been operated on. SIMPSON recognises the difficulties inherent in the statistical assessment and acknowledges that this series lacks any planned control, but feels that even so certain conclusions are justifiable. He expresses the opinion that this and the three American [9 14 15 18] series indicate that operation provides a worth-while improvement in prognosis for women with myasthenia, particularly by reducing case-mortality. In the London series women had a mortality of 15·4% from myasthenia or postoperative causes; and this certainly compares very favourably with the figure of 28·8% for deaths in the unoperated group. The figures for males suggest that operation reduced mortality hardly at all. As to the status of the survivors, it is clear that this differs widely at any given time both in the operated and in the unoperated. SIMPSON finds that in those not operated on mortality is higher in females than males, and that fewer women reach the higher categories of activity; whereas in those who have been operated on this trend is completely reversed. It seems that a shorter preoperative duration is likely to result in a higher physical status among survivors, but has little or no influence on the risk of death after operation.

With each new case of myasthenia the clinician must face the problem of whether to advise thymectomy or not in that particular instance. FERGUSON et al.,[10] reporting the results of the medical management of 75 patients, commented on the benign course of the ocular type of myasthenia—to which attention had been previously drawn by GROB,[9] who had followed 48 such cases for an average period of 8·5 years without encountering a single death. OSSERMANN et al.[19] suggest that juvenile cases of myasthenia gravis and those with highly localised manifestations do not need thymectomy, whereas the more generalised and acute types, progressive and unresponsive to medical treatment, may be submitted for thymectomy; but they do not give figures to indicate results. In the light of the present evidence it seems reasonable to conclude that young females with generalised myasthenia of short duration should be regarded as eminently suitable for operation, since among them operation results, in a significant saving in life and a lasting improvement in the myasthenic state. At the other end of the scale the patient with ocular myasthenia which has not spread to the general musculature within two or three years is likely to carry on quite well under medical management, and may in fact have a long spontaneous remission. When a tumour is present, radiotherapy will usually be preferred, though some workers recommend radiotherapy followed by operation. For the remainder it is impossible to generalise; the therapeutic plan will be conditioned by the personal views of the clinician, and by the patient's age, occupational and social circumstances, and personal wishes.

18. Schwab, R. S., Leland, C. C. *J. Amer. med. Ass.* 1953, **153**, 127

19. Osserman, K. E., Kornfield, P., Cohen, E., Genkins, G., Mendelow, H., Goldberg, H., Windsley, H., Kaplan, L. I. *Arch. Neurol. Psychiat.* 1958, **102**, 72.

Annotations

UNEXPECTED DEATH IN INFANCY

IN infancy unexpected deaths have a special importance because of the distress they cause, often including tragic self-reproach by the parents. Though, by their very nature, they must commonly be unavoidable, even a small reduction in their number would be very well worth achieving. But better preventive measures must wait on better understanding of the reasons why babies die unexpectedly, and this is most likely to come from carefully planned studies by teams of experts. The inquiry into "sudden death" in infancy, organised by Prof. Leslie Banks, of Cambridge, at the request of the Ministry of Health, is therefore welcome, and his interim report, describing the work arranged by the very knowledgeable steering committee,[1] will command attention.

It describes, in fact, only a pilot investigation made in selected London areas, and in Cambridge and the surrounding district, during the two years ended March, 1956. Moreover, since the main object was to gain experience for use in the subsequent full-scale investigation, alterations were made from time to time in the method of inquiry, in the routine for collecting material, and in the forms used for recording information. Hence what we are now given is to be regarded as no more than a report on progress, and its chief value lies in indicating the means by which such an inquiry may best be pursued and the lines of research which are likely to be most rewarding.

It is based on a study of 81 cases of sudden death between the ages of 2 weeks and 2 years, and the information obtained is considered in its pathological, microbiological, and social aspects. 64 of the infants died in London and 17 in the Cambridge area. In 38 of the 52 London infants examined histologically, evidence of tracheobronchitis was found, and in a proportion of these cases a special technique, not described in the paper, was used to demonstrate a characteristic tracheobronchial lesion. The tracheobronchitis was regarded as possibly of viral origin, but viruses were actually isolated in only 2 of 50 infants examined for them. The remaining 14 London infants who were examined histologically had purulent respiratory infections, septicæmia, or gastroenteritis. In contrast, no definite "cause of death" was found in 13 of the 17 Cambridge cases, while infections (bronchiolitis, bronchopneumonia, septicæmia) were found in the other 4. Though the report does not compare the two series in detail, it seems possible that the London group of infants who had tracheobronchitis was similar to the Cambridge group in whom the cause of death was uncertain, and that the disparity in findings was due to differences in histological technique. On the other hand, the Cambridge workers may have been dealing with quite another problem, since the two groups differed (though perhaps not significantly) in sex-incidence, seasonal incidence, and the proportion of sudden deaths to all deaths at this time of life. It would be interesting to know more

1. Banks, A. L. *Mon. Bull. Minist. Hlth Lab. Serv.* August, 1958, p. 182.

about the criteria for diagnosing "tracheobronchitis, possibly of viral origin" in the London infants, since interpretation of histological changes is always to some extent subjective.[2 3]

Bacteriological studies were made in 66 of the 81 cases, and in about half of these the lungs were sterile on culture or contained only the normal flora of the upper respiratory tract. In most of the other cases, gastrointestinal organisms were cultured from the lungs, but the meaning of their presence is doubtful, since postmortem contamination could not be excluded. Pathogenic organisms, including *Staphylococcus aureus* and *Hæmophilus influenzæ*, were found in 9 of the 66 cases. The only conclusion drawn from the microbiological evidence was that infection with pathogenic bacteria is probably not an important factor in causing sudden death in infancy.

Various workers have found a higher incidence of unexpected deaths during the winter months, and a preponderance of male infants.[4] In the present inquiry both these observations were confirmed for the series as a whole and for the London series, though not for the smaller Cambridge series, in which the sex-incidence was roughly equal and cases occurred almost uniformly throughout the year. The report suggests that poor general health, premature birth, illegitimacy, poor maternal care, or poor social circumstances, while not causes of sudden death, may increase the risk: one or more of such handicaps was recorded in 44% of cases. Accidental suffocation in a soft pillow or by overlaying caused few if any of these deaths, but the possibility that a considerable proportion followed the inhalation of food or vomit could not be excluded.

A remarkable statement in the social section of the report is that cases of sudden death formed 25% of all deaths in the age-group and that in Cambridge the figure was as high as 44%. This high proportion raises the question whether all these so-called sudden deaths would ordinarily be regarded as unexpected deaths. Data from the Registrar General showed that, in 1955, 20·5% of deaths between the ages of 2 weeks and 2 years were "certified by a Coroner as being due to influenza, pneumonia, bronchitis, or other respiratory cause, or as due to obstruction, inhalation, ingestion, or accidental mechanical suffocation". Professor Banks' report says that these deaths are comparable to those considered in the inquiry, but this seems arguable. For example, deaths due to ingestion would presumably include cases of accidental poisoning, whereas other accidents, such as road accidents, are considered as "clearly outside the scope of the investigation". The full account of this study could usefully define more precisely what is meant by the terms "sudden death" and "unexpected death" in infancy.

The general conclusions of the committee so far are in line with most previous work in suggesting that, while the causes of sudden death in infancy are largely unknown, mechanical factors such as overlaying and accidental suffocation are comparatively rarely responsible, while respiratory infection, possibly by a virus, is an important factor in most cases. Nothing emerged from the pilot investigation to explain why apparently mild infections should cause death in these infants, and this is perhaps the crux of the problem.[3] The results of the main investigation, based as it is on so much careful and methodical preparation, will be eagerly awaited.

2. Skogrand, A. *Acta path. microbiol. scand.* 1957, **41**, 486.
3. Stowens, D. *Amer. J. Dis. Child.* 1957, **94**, 674.
4. Barrett, A. M. *in* Recent Advances in Paediatrics (edited by D. Gairdner). London, 1954.

CARPAL BOSSING

CARPAL bossing was first described by Fiolle [5] in 1931, and since then the condition has rarely been noted outside France. It consists of a painful prominence of the dorsum of the base of the third metacarpal and capitate, visible on radiographs as a small exostosis and containing bone. Most patients present with aching pain, a detectable bony lump, sometimes a bursa, and sometimes difficulties with snapping extensor tendons. Recurrences after removal seem to be common.[6] The single case described by Dorosin and Davis [7] and the two cases of Menegaux [8] suggest that this is a rare disorder. In a small investigation of normal subjects Larson et al.[9] have now shown that prominence of the third metatarsal base was rare in children but common in adults, and present in 50% of physiotherapists. They suggest that the boss is due to new bone formation resulting from use. It is clear that the deformity is common, but symptoms are rare, and treatment should depend on whether it is causing inconvenience.

FOOD AND VOMIT IN THE LUNGS

THE aspiration of food and vomit has been investigated by Gardner.[10] He introduced barium sulphate through a gastric tube into the stomachs of ten patients immediately after death. The bodies were then transferred to the mortuary, and radiographs of the lungs were taken at the subsequent necropsies. In seven out of the ten, barium had entered the lungs, reaching the alveoli in several. Thus, unless the trachea is blocked as soon as the patient dies, necropsy evidence of antemortem aspiration cannot of itself be considered conclusive.

Gardner then studied a series of ninety-four adult male and female patients who had either undergone a major operation or were debilitated for other reasons. Each had non-flocculable barium sulphate added to all drinks—in the proportion of one part in six—for two to four days. The lungs were repeatedly examined radiographically, and bronchoscopy was undertaken when clinically indicated. Barium entered the lungs of ten patients (11%), but in most of them it was impossible to decide whether it was inhaled during vomiting or feeding.

To distinguish the incidence of aspiration of vomit from that of aspiration of food, barium was given to a further fifty-one patients directly into the stomach through a tube, so that its appearance in the lungs could be due only to inhalation of gastric contents. This occurred in only one patient. Gardner concludes that aspiration of food is commoner than that of vomit (it took place probably in 9–10% of the patients studied as opposed to 1–2% for vomit)—and that it is often multiple. Aspiration of either is often extremely difficult to diagnose clinically. The overall results suggest that one in about every ten debilitated surgical patients inhales food or vomit.

The complications directly attributable to aspiration are difficult to assess; but the fact that some patients in this

5. Fiolle, J. *Bull. Soc. nat. Chir.* 1931, **57**, 1687; *ibid.* 1932, **58**, 48.
6. Carter, R. M. *J. Bone Jt Surg.* 1941, **23**, 935.
7. Dorosin, N., Davis, J. G. *Radiology*, 1956, **66**, 234.
8. Menegaux, G. *Rev. Orthopéd.* 1934, **21**, 231.
9. Larson, R. L., Lazeano, M. A., Janes, J. M. *Proc. Mayo Clin.* 1958, **33**, 337.
10. Gardner, A. M. N. *Quart. J. Med.* 1958, **27**, 227.

series undoubtedly died as a result of aspiration suggests that greater care is needed in posturing and feeding those who are very ill. Gardner believes that aspiration of vomit or food is too often the coup-de-grâce—rather than an agonal phenomenon—in an ill patient who might otherwise recover. He suggests that the standard hospital feeding cup, which is designed to facilitate feeding in recumbency, should be abolished as its style contributes to aspiration. Not only does the shape of the spout enable fluid to be poured into the trachea, but the hooded top ensures that the patient is taken unawares. The patient should either sit up and drink out of an ordinary cup or glass or lie on his side and drink through a straw. If neither is practicable, feeding should be through a tube directly into the stomach. The danger associated with vomiting can be offset only by the adoption of a prone or semiprone position.

OCCLUSION OF ANTERIOR SPINAL ARTERY

THE syndrome of occlusion of the anterior spinal artery is of interest because of the striking clinical picture. It was first recorded in life by Spiller,[1] who called the disorder syphilitic acute anterior poliomyelitis, having recognised the distinctive involvement of anterior horn cells at the level of the lesion. This description of the necropsy findings is excellent. For many years the condition continued to be regarded as a manifestation of syphilitic vascular disease; but it is now clear that many patients show no evidence of neurosyphilis; indeed the cerebrospinal fluid is often normal.

Ten cases seen at the Mayo Clinic since 1949 have been described by Peterman et al.[2] In three the lesion involved the lower cervical region, and in seven the thoracic region of the spinal cord. The onset is usually abrupt and the clinical picture is fully developed within a few hours. In the lower limbs, there is sudden loss of power often with pain across the shoulders; bladder and bowels are paralysed; and appreciation of pain and temperature is lost below the level of the lesion. The posterior columns, subserving joint-position sense, touch, and vibration sensibility are spared. In the cervical cases there are total lower-motor-neurone lesions of the muscles supplied by the segments involved—usually C7, C8, and T1. There may therefore be very severe permanent disability due to bilateral disruption of function of the upper limbs, particularly the hands. In addition there may be segmental sensory loss, presumably due to ischæmia in the central grey matter of the cord. Symptoms and signs are usually symmetrical. The association of an anterior-horn-cell disorder at the level of the lesion with sparing of the posterior columns points to the diagnosis.

The outlook for the lower limbs is fair. In all but one of the ten Mayo Clinic cases the patient could walk after a few weeks; and control of bladder and bowels was regained. Wasted muscles do not recover. The anterior horn cells, which seem to be extremely vulnerable to anoxia, are permanently affected.

Woollam and Millen[3] agree with Feeney and Watterson[4] that the nervous system has been developed to the limit of the vascular supply: hence the havoc brought about by occlusion of the anterior spinal artery. Radicular arteries from vessels adjoining the vertebral column vary from two to seventeen; and two of these (one cervical and one lumbar) contribute largely to the anterior spinal artery, which is formed by the fusion of two longitudinal chains. The artery supplies the whole of the grey matter except part of the dorsal horn, and it partly supplies the anterior columns of white matter. The lower cervical region and the lower thoracic region are most usually involved. The reasons for this are not clear. It is believed that blood flows through the anterior spinal artery, from both above and below, towards the thoracic region, and the sites of election may be watersheds. Another possibility is indicated by clinical considerations. Some patients with occlusion of this artery show no evidence of generalised vascular disease or of disease of the vertebral column. Some seem to have engaged previously in physical work involving the shoulders and back, or to have suffered exposure. The dependence of the anterior spinal artery on radicular contributions suggests that vasodilation in the thoracic muscles may lead to ischæmia in the spinal cord. The converse situation has been described in which the anterior spinal artery participated in the anastomosis consequent on coarctation of the aorta at the level of the ductus arteriosus.[5]

In other conditions associated with vascular lesions of the cord, such as syphilis, vertebral fracture, aortic occlusion during operation, dissecting aneurysm of the aorta, and the aortic-arch syndrome, there are obvious pathological reasons for cord involvement. In many cases of occlusion of the anterior spinal artery this is not so: it is not even clear whether hypertension and atherosclerosis are important in this disorder. The description of well-documented cases is still of great interest.

"CLEAN" VERSUS CATHETER SPECIMENS OF URINE

IT is widely accepted that specimens of urine for bacteriological investigation from female patients should be obtained by catheterisation. Besides causing inconvenience and occasionally embarrassment, this procedure carries a moderate risk of introducing fresh infection, and in fact it is often carelessly performed without regard for asepsis. It has been suggested that technical perfection necessitates the presence of two nurses—one to separate the labia and clean the meatus, and the other to insert the catheter.

Wishing to avoid the hazard of introducing infection Boshell and Sanford[6] advocate the examination of "clean" freshly voided specimens as an alternative, and claim that these specimens compare favourably in a bacteriological sense with those obtained by catheter. The suggested procedure consists in thorough cleaning of the periurethral area in a Sitz chair filled with green soap solution, followed by gentle scrubbing with pads containing 'Zephiran' (1% solution of benzalkonium chloride). The patient then voids, holding the labia apart, and a mid-stream specimen is collected for culture. The results in 67 cases corresponded closely with those from subsequent catheter specimens, and the technique is recommended as a screening method to reduce the need for instrumentation. It may be questionable, however, how far such arrangements are appropriate in a busy outpatient clinic or hospital ward.

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Special Articles

TREATMENT OF BREAST CANCER
THE QUESTION OF "SELECTION"

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The Lancet of May 31 carries a letter by Ian Mackenzie which relates to the comparison of the five-year survival-rate for a group of patients treated at the Mayo Clinic by radical mastectomy [1] with the five-year rate for a group of patients treated at Edinburgh [7] by simple mastectomy and radiotherapy. A previous letter from George Crile, Jr.,[2] referred to by Dr. Mackenzie, deals with the same matter, as do several other letters.

Comment on the comparison can be misleading without an explanation of the context of the analyses.

CRITICISM OF RADICAL MASTECTOMY

The report from the Mayo Clinic, in its primary section, set forth the results, in the form of survival-rates, for a group of 9649 patients with mammary cancer who had been treated surgically over a period of almost half a century, from 1910 to 1954. In all but a negligibly few cases the treatment was by the classical radical mastectomy of Halsted (supplemented in designated cases by irradiation).

In the last couple of decades radical mastectomy has come under severe criticism. In particular, McWhirter's [4 7] analysis of its putative deficiencies has led him to conclude that it should be abandoned. Since 1941, under his direction, patients at Edinburgh have been treated instead by simple mastectomy and radiotherapy, with results [4–7] which he regards as better. His reports have had a significant influence in the United States, and, though the superiority of simple mastectomy and irradiation has not been explicitly accepted, his arguments have undermined confidence in radical mastectomy. Surgeons whose training and experience do not permit them to perform the radical operation have found in them support for performing only simple mastectomy, and some therapeutic nihilists have found support for arguing even that all treatment of cancer of the breast is futile. These views have permeated to young physicians beginning their careers and (even more important) to the general public, and the effect has been confusing and demoralising. Veritably an ominous situation was developing. Since our own results with radical mastectomy, though not ideal, did not reflect the dire predictions of McWhirter's theoretical analysis, we felt obliged to make a careful examination of his reports. In the second section of our article we presented a critical analysis based on this examination.

We may remark, with entire objectivity, that this examination was undertaken with no animus toward Dr. McWhirter or bias against his bold experiment. On the contrary, we all had been impressed with the admirable thoroughness of its implementation, and the simple clarity and completeness of his statistical reports. More than once, one or other of us actively participated in making an opportunity for Dr. McWhirter to present his case. However, it is necessary to note that systematic reading of his articles reveals a disquieting characteristic in them: whenever he had occasion to refer to favourable results obtained with radical mastectomy, he explicitly imputed "selection" to that series. Thus, writing of a report of Harrington, he said: "Some degree of selection may be presumed, for in 40% of the cases microscopic examination of the axillary glands did not show involvement." [4] Now it is not obvious why an incidence of 60% with axillary metastasis should imply "selection". In fact, the choice of this statistic as evidence of "selection", proved an unhappy one, for another paper [7] stated that when radical mastectomy was performed in Edinburgh before 1941, the proportion of cases found with axillary metastasis was just 60%. The imputation of selection is sometimes couched in terms suggesting prejudice, as when McWhirter [4] said:

> "Unfortunately the extent of failure of the radical operation is too often concealed by presenting only the results obtained in highly selected cases. By selecting cases for the radical operation very carefully and by publishing the results only in the cases so selected the survival rates may be made to appear so good . . ."

Or again [6]:

> "There is no more certain method of securing good results than by careful selection of patients for treatment . . . it is not uncommon to limit the use of a method to early cases and to apply some alternative method in the more advanced cases. Thus as the limitations of radical mastectomy become more clearly recognised, it has become customary to restrict the operation to early cases and to refer all the more advanced cases for treatment by roentgenotherapy."

The last statement is fairly in reverse of the experience of the Mayo Clinic, where radical mastectomy has been the undeviating basic policy of treatment, and the proportion of patients found inoperable has been in steady decline. It appears also to be in contradiction of general experience, as reflected in a recent report from Connecticut,[9] where it was found that use of the radical operation is increasing, radiotherapy decreasing, and the survival-rate improving.

In reaching his conclusion that simple mastectomy and irradiation is superior McWhirter did not compare his results with those of contemporary treatment by radical mastectomy. He compared them with those of radical mastectomy as practised in Edinburgh before this new treatment policy was instituted. The chief part of our critique of McWhirter's report consisted in an analysis of the fallaciousness of this comparison, with its reasoning *post hoc ergo propter hoc*. Our own results from the Mayo Clinic over the long period studied, during which there was no material change of treatment, showed progressive improvement. So did other results quoted from the literature; and (as could be fairly clearly demonstrated from the admirably detailed statistics given in McWhirter's early reports) the results in Edinburgh also show improvement which was independent of change of treatment. As is apparent from independent evidence, this improvement is mainly due to patients coming for treatment earlier in the disease—a result, we believe, of the cancer-education campaign by "lay" organisations. Our point here, then, is this: McWhirter's claim that simple mastectomy with irradiation is better than radical mastectomy was based on a fallacious demonstration.

EDINBURGH AND ROCHESTER

It was natural, however, that we should try to compare our results with those reported by McWhirter. We were

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very conscious that the results in the two series, taken on their face, were not validly comparable. In particular, since we had noted an improvement in our results with time, and since a similar improvement could reasonably be assumed in McWhirter's experience, it would not be "fair" to include results of our experience later than those represented in his report. We segregated our cases in which treatment was given in the same years as those reported by McWhirter—namely, 1941–47. Now what cases of these years should be included? McWhirter often stresses that all cases should be included. But we thought this should mean all cases "coming under treatment within the respective treatment policy". In making comparative studies this is what is generally done, and it seems to be what McWhirter does. In his table V,[7] all the cases (1882) are included, segregated into several groups, but this is a bookkeeping table. In table VI, which is concerned with the influence of age on survival, cases categorised as having distant metastases are omitted. Here McWhirter is proceeding as one normally does—for purposes of comparative analysis one uses only the treated patients. We included only his 1609 cases without distant metastases (1882 less 273 having distant metastases) to represent his series coming under treatment; but of course we included *all* of them. The results in these cases were compared with the results in *all* our cases in which radical mastectomy was performed during the same period, which numbered 1918. It is this comparison that is being brought into question.

We believe this comparison, using only the patients coming under treatment, is the most meaningful one; but in present circumstances we think it to the point to make the comparison including literally all patients—i.e., including McWhirter's 273 patients (15%) who did not come under treatment, and the 362 patients (16%) in the Rochester series found inoperable, that is, patients who did not have a radical mastectomy because of the advanced character of the cancer. There is a mechanical difficulty here, because in Rochester we do not regularly follow up the untreated patients, and so we do not know the number of five-year survivals among them. We made the calculation on the assumption that the survival-rate among these inoperable cases was 4·4%, which is the survival-rate recorded by McWhirter for the comparable 273 cases of his series; we also present the figures assuming that this survival-rate was zero. The results are shown in the accompanying table. Whichever way the comparison is made—for the entire series or for the group representing the treated patients—the conclusion is essentially the same. The five-year survival-rate for the patients dealt with under the policy of radical mastectomy exceeds that for the patients dealt with under the policy of simple mastectomy and irradiation: it exceeds it by what amounts to about 20% of the survivals achieved in Edinburgh. Recalling McWhirter's reiterated emphasis on selection, we may note that in a review [9] of all (i.e., unselected) cases of cancer of the breast in Connecticut in 1941–47, the five-year survival-rate averaged 51·3%; for the Edinburgh series in the same years it was 41·8%.

COMPARISON OF FIVE-YEAR SURVIVALS, TREATED AND TOTAL SERIES

Patients	Edinburgh		Mayo Clinic		
	No.	Lived 5 years or more	No.	Lived 5 years or more	
		No.		No.	No.
Subjected to treatment policy*	1609	774(*48·1*%)	1900‡	1127 (*59·3*%)‖	1127 (*59·3*%)
Not subjected to treatment policy†	273	12 (*4·4*%)	362	16§ (*4·4*%)	0¶ (*0*)
Total ..	1882	786(*41·8*%)	2262‡	1143 (*50·5*%)	1127(*49·8*%)

* In this group, as respects both series, are included the patients used in the original comparison.
† For the Mayo Clinic series, these are the patients not receiving radical mastectomy; for McWhirter's series, they are the patients "with distant metastases present".
‡ 18 patients not traced for five years are omitted.
§ Assume 4·4% survived.
‖ Adjustment for hospital death-rate of 0·6% will lower this to 58·9%.
¶ Assume none survived.

Does this establish definitely that radical mastectomy has a higher survival-rate than simple mastectomy with irradiation? In particular can we be certain that the Edinburgh series as a whole, or the group of patients coming under treatment, is not generally of a more advanced cancer? We did not say so. We described the problem of the comparability of cases as "the devil's own question". We carefully considered the data that bore on it, and concluded that the two series could reasonably be regarded as fairly comparable. But in the end we wrote [1]:

"But when all is said, on this matter of the selectivity of the cases, that can be said, it must be admitted that we really do not know with certainty how important a factor it is in accounting for the difference in survival rates reported in the literature. We agree with Atkins that, in order to evaluate the relative efficacy of radical mastectomy and the projected policy favoring simple mastectomy with radiotherapy, McWhirter missed an opportunity to initiate a controlled clinical trial . . ."

What is the burden of Dr. Crile's criticism, which is a replica of the criticism made by Dr. McWhirter himself, in some personal communications received before publication of Dr. Crile's letter? In essence it is that the Mayo Clinic cases are favourably selected; specifically it is that we should not have used the total 1609 cases of McWhirter's series as we did. It is suggested that we should, instead, have used only the 1063 cases which he enumerated under the rubric "operable"—which here means operable by radical mastectomy, an operation not performed in Edinburgh. These 1063, however, constitute only 56% of the total 1882 of McWhirter's series,† and it is suggested that they are the ones that should be compared with our 1918 cases treated by radical mastectomy, which constitute 84% of the total 2280 of the Mayo Clinic series (table). This is hardly in keeping with McWhirter's repeated admonitions that, in reporting results, all cases should be included. The 546 cases of his series which he would have us omit on the ground that at the Mayo Clinic they would be regarded as too advanced for radical mastectomy, are enumerated under the rubric "locally advanced"—defined as having "complete fixation of the primary tumour to the pectoral fascia or to the ribs, fixed nodes in the axilla, enlarged supraclavicular nodes or widespread involvement of the

† To accept this suggestion would imply that, among women with mammary cancer who come from South East Scotland to Edinburgh for treatment, the disease is so far advanced that it is "inoperable for radical mastectomy" in 44% of cases. This would be a severe indictment of cancer education in that country in respect of early recognition and treatment, if it does not, instead, imply a conception of inoperability which reflects an extreme prejudice against radical mastectomy. McWhirter's conception of the effectiveness of this operation is clearly given when he says [4]: "When radical surgery is the only method of treatment available and when all cases coming (whether admitted or not) to a large general hospital are considered I do not believe the five-year survival rate will be found to be higher than 20% to 25%." The validity of his estimate may be gauged by contrasting it with the results reported [9] for the general population of Connecticut.

cutaneous lymphatics over the breast, but no evidence of more distant metastases ".[7]

Such definitions are fairly easy to formulate but very difficult to apply in a uniform standard way, even within a single clinic—much less in different institutions in different countries.‡ The indications for radical mastectomy at the Mayo Clinic are very generous, and we believe that we perform this operation regularly with patients who would be placed in the above category. In at least one publication[4] McWhirter considered cases of Manchester stage III as operable; and such cases comprise about half of those he includes in the category "locally advanced", though they do not correspond to the quoted definition of this category. This will illustrate the element of arbitrariness inherent in deciding which cases are "inoperable for radical mastectomy". A proposal[8] to institute an international classification of stages is, in theory, sound. But if the classification is to be used for standardising the comparison of survival results, it may in practice introduce more confusion than clarification. If method A has a better survival record than method B for all cases, but method B has equal or almost equal results for the cases classified as "operable", then the general problem of comparability is complicated by the additional problem of applying the classification uniformly. If the criteria of "operable" have been defined in the first instance by an advocate of B, then the task becomes perplexing indeed. It is only human that an advocate of B should think that a particular patient who is not likely to do well by that method would certainly not do well by A. Better results with A, except in a controlled experiment, cannot be considered proof that A is really the preferable method to use invariably; many other elements have to be taken into account. But the argument that method B's inferior results automatically prove that patients subjected to method A are selected is not acceptable.§ In our analysis of the Mayo Clinic series, the designation of a case as "inoperable", for purposes of computing an inoperability rate, is not an expression of opinion about its suitability for operation: it means that radical mastectomy was not in fact performed. Likewise, we did not refer to cases which were "operable" but only to patients who were operated upon by radical mastectomy.

The suggestion that our cases should be compared only with the 56% of McWhirter's series enumerated under the rubric "operable" is reminiscent of a procedure occasionally used by physicians, by which a method of therapy is advocated as effective but "only in properly selected cases". Results are then presented, but only for the properly "selected cases". We do not think this is a good procedure; we think that all patients coming under treatment should be included.

‡ To gauge the difficulty of setting up a *workable* classification of the advancement of disease, even in the relatively objective situation of the reading of X-ray films, one may profitably study an article[9] by Newell, Chamberlain, and Rigler, entitled Descriptive Classification of Pulmonary Shadows.

§ McWhirter has presented a semantic case against radical mastectomy which is well-nigh invulnerable. He begins with the premise that radical mastectomy must fail in a large majority of cases, variously estimated as from 64% to 80%.[4 6 7] If now one presents favourable results with radical mastectomy, it only makes the case worse for radical mastectomy. Because—so the argument goes—since we know that radical mastectomy is an ineffective operation, then favourable results reported with radical mastectomy can be the result only of the surgeon's selecting the early cases and passing on the advanced cases to the röntgenologist for palliative treatment. Now the surgeon would not do this if the operation were effective. Hence, in this argument, good results prove the ineffectiveness of the operation.

The Mayo Clinic series, taken as a whole, may in a sense be considered "selected". The practice of this clinic is, to a considerable degree, a referred one, and patients are referred for treatment from all parts of the country. But when local doctors make selection between patients with early or advanced disease, it is those with the more advanced disease and less hopeful outlook who are selected for referral; and our clinic is sometimes dubbed as a "court of last resort". The patients who come for treatment represent a wide spectrum of degrees of advancement of the cancer. Early cases do appear, and happily the proportion of patients coming for treatment early in the disease is increasing—a result, we believe, of the cancer educational campaign. But very advanced cases are also received, including moribund patients, in no small number, admitted to the hospital only to die there. It is necessary to make this rather graceless statement, because in some quarters our results in cancer of the breast are disregarded on the ground that we deal only with "selected" early cases. If, because of this misconception, erroneous judgment is made as to the relative efficacy of different methods of treatment, it is the patients who will be the victims.

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Occasional Survey

INFECTION ACROSS THE INTACT CONJUNCTIVA

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THE mounting evidence that the conjunctiva may be the route of natural infection in certain virus and bacterial diseases seems to have attracted little attention.

The first practical application of this concept was in North Africa. In 1930 Anderson and Gerard,[1] in a preliminary experiment, instilled convalescent serum into the eyes of 30 contacts of measles three times daily for eight days, and none developed measles during eighteen days of observation; no controls were mentioned and no further report has been traced. A few years later Sicart[2] attempted to control an outbreak of measles in a residential school by the method of Anderson and Gerard, but out of 24 contacts treated 11 developed measles. As the latter were in the sixth day of the incubation period when the instillations were started, this failure is not surprising.

In 1954 Karola Papp[3] put the matter on a more scientific basis. She transmitted measles across the intact conjunctiva in 5 out of 6 susceptible children by means of saliva taken from cases of measles in the first three days of the eruption. On the other hand, no result was obtained in 9 susceptible children whose buccal mucosa and tonsils were painted with infective measles saliva; and only 2 out of 13 such children developed measles when the infective

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2. Sicart, M. *ibid.* 1936-37, **26**, 266.
3. Papp, K. *Rev. Immunol.* 1954, **18** 380.

saliva was instilled into the nose. In all these cases the saliva was well diluted with normal saline. With the same technique in mumps 2 positive results in 10 trials were reported, but failure resulted in 6 cases out of 6 when the infective mumps saliva was painted on the buccal mucosa and tonsils. Rubella was similarly transmitted across the conjunctiva in 2 cases out of 6; but no success was obtained with chickenpox transmission in 21 instances, both saliva and fluid from vesicles being used. None of these instillations produced any local reaction.

Papp pointed out that the fine superficial capillary network in the conjunctiva, draining into the deep network by relatively large venous channels, probably favoured absorption of infectious material; in contrast, the capillary network in the nasal mucosa was much coarser, one of its main functions being to warm the inspired air. She also suggested that the success of the experiments of Anderson [4] in transmitting rubella by infectious material sprayed into the mouth, might be due to the infection reaching the eyes as well as the mouth.

Papp [5] next attempted to prove that the eye was the *sole* route of natural infection in measles. In each of three trials, 3 susceptible children, whose eyes were completely protected by goggles closely sealed to the face, were placed in contact with highly infectious cases of measles, and *none of these contacts developed measles*. Although this experiment was uncontrolled, the very high infectivity of measles in the early acute stage makes this result indeed remarkable. In a second experiment four groups, totalling 18 susceptible children, after exposure to undoubted measles infection, had one drop of convalescent serum instilled into each eye—in 15 cases one to six hours after exposure to the infection; *none of these 15 children developed measles*. In the remaining 3 cases, where the instillations were made seventeen to twenty-four hours after exposure, 2 developed modified, and 1 unmodified, measles.

This year Rusti [6] has reported strikingly successful results with Papp's method in the prophylaxis of measles, mumps, and chickenpox, when these infections were introduced into a children's sanatorium containing many susceptibles. Of 69 children believed to be non-immune, all were protected from measles, as well as 58 from chickenpox in one experiment and 29 in another, and 57 from mumps in one experiment and 61 in another. Moreover 12, believed to be susceptible to both mumps and chickenpox, when exposed to both diseases, contracted neither. The only failure reported was among 22 children exposed to 2 different cases of chickenpox on successive days; in this group 2 developed chickenpox on the seventeenth day. Unfortunately none of these massive experiments were controlled.

Relevant controlled experiments in guineapigs have recently been reported by Moore.[7] He has produced striking quantitative evidence that the conjunctival route is far more effective than the oral route in producing systemic salmonella infection. This finding was confirmed by exposing animals wearing effectively sealed goggles, and also control ungoggled animals, to environments heavily contaminated with *Salmonella enteritidis*; the former were found to be highly resistant to infection, while the ungoggled controls showed high infection-rates. It was also found that conjunctival swabbing was more effective than rectal swabs for detecting the spread of this infection; and eye-swabbing combined with segregation of eye-positive guineapigs and their cage-mates was apparently successful in controlling two *Salm. enteritidis* epizootics. Moore's final remark seems to me to deserve wide publicity: "It may well be that the conjunctival route is worth considering in the epidemiology of bacterial and virus infections of man."

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Congresses

GENETICS

THE Tenth International Congress of Genetics was held in Montreal on Aug. 20–27.

Population Genetics

T. EDWARD REED (Ann Arbor, Michigan) discussed the stability of Huntington's chorea. It had been suggested that the condition may be increasing as afflicted persons were more than usually fertile. This inference was erroneous, and support for it was due to the fallacy of regarding the unaffected siblings as a suitable control. Not only would they not know that they would be unaffected at their period of highest fertility, but they would also tend to be younger. A comparison of the fertility of persons with Huntington's chorea and the remainder of the population standardised for age showed that the carriers of the gene were not producing children at as high a rate as the remainder of the population of Michigan.

JESSICA H. LEWIS and C. C. LI (Pittsburgh, Pennsylvania) presented data on the families of persons with hæmophilia A and B. Type A, which represented 84% of the 116 cases, was the classical hæmophilia; type B was sometimes known as Christmas disease. There was strongly suggestive evidence of a disturbed sex ratio, and also a disturbed segregation ratio of the defective gene; in each case the disturbance was such as to increase the dissemination of the harmful gene, and a gene which could load its chance of segregation could be stable although disturbing the viability of its host.

Cytology

T. T. PUCK (Denver, Colorado) demonstrated the feasibility of culturing human cells derived from minute skin-biopsy specimens. These cells remain in good health for months, and a 20-hour division cycle provides unlimited numbers; the chromosomes retain their individuality, and colchicine inhibition makes their detailed study practicable. The elaboration of suitable media should allow chromosomal investigation to be made from material acquired and cultured with the simplicity of a throat swab.

Using these methods of culture, J. H. TJIO (Zaragoza, Spain) and also E. H. Y. CHU and N. H. GILES (Yale) have made extensive studies of the chromosomal complement in man. No cells showing 48 chromosomes were observed. In subsequent discussion of these papers J. L. HAMERTON (London, England) suggested that, in view of the consistent preponderance of expert opinion, and the absence of public evidence to the contrary, 46 should be regarded as the basic chromosome number in man. TJIO and CHU claim that the individual chromosomes in man can be distinguished, and they have each advanced a separate nomenclature.

B. M. SLIZYNSKI (Edinburgh) presented data on the frequency of chiasmata in the oocytes and spermatocytes of mice; chiasmata are about 15% more frequent in the female, implying a slightly looser linkage.

A. BAJER and J. BAJER-MOLÉ (Cracow, Poland) showed a film of mitosis in living plant cells, including detailed studies of normal mitosis followed by the aberrations induced by irradiation and colchicine. The mechanism of mitosis, which is similar in all the higher plants and animals, has not previously been demonstrated at such a standard of technical excellence.

Colour-blindness

H. KALMUS (London, England) showed a film revealing the world as it looks to the colour-blind. The film was made under the direction of a woman colour-blind in one eye.

New Individualities of the Blood

SYLVIA LAWLER (London) presented data confirming the specificity of Gm serum-protein groups in man. A Gm-positive serum is defined as that which will inhibit the agglutination of specially sensitised red cells by the serum of patients with rheumatoid arthritis. Data from numerous families were consistent with inheritance as a single factor, active in the heterozygote, and not closely linked with other blood-group loci.

O. SMITHIES (Toronto) presented an extensive series of two-dimensional starch-gel electrophoretic blocks demonstrating previously unrecognised variation in the constituents of the β-globulin fraction of the plasma. While almost all Canadians tested showed only one type (C), a very few having type B also, a high prevalence of type D was found in a sample of Australian aborigines, and some specimens showing this type were obtained from New York Negroes. Three alleles are postulated, and these appear to segregate independently of those determining the major blood-groups. There is highly suggestive evidence of identity between these β-globulins and transferrin.

Blood-groups and Disease

C. A. CLARKE and P. M. SHEPPARD (Liverpool) presented their extensive data on the blood-group and secretor status of siblings of patients with duodenal ulcer. The increased liability of group-O persons and of non-secretors to duodenal ulcer could not be demonstrated within these family groups. The apparent partial protection enjoyed by secretors is unlikely to be a non-specific effect of swallowing polysaccharides, as the quantity in the saliva of non-secretors, estimated by the fucose method, is almost as high as in secretors. Specific absorption of ABO antibodies could be demonstrated on the exfoliated duodenal cells of secretors.

Clarke and Sheppard also presented extensive data consistent with the hypothesis that the common form of erythroblastosis fœtalis is consequent on a previous pregnancy in which the baby was both rhesus-positive and compatible as a donor to the mother relative to the ABO system.

J. BUETTNER-JANUSCH, S. J. BEHRMANN, and F. P. THIEME (Ann Arbor, Michigan) had studied the ABO blood-group and the secretor status of the saliva and semen, using McNeill's techniques, of apparently sterile men. Defining an aberrant secretor as a man not secreting in his semen at least one of the ABO(H) substances present in his saliva, a high proportion of aberrant secretors were found in sterile men, many of whom showed defective spermatogenesis. None was found in a sample of fertile men. Evidence was also presented suggesting that husband-wife ABO incompatibility may be a cause of infertility or reduced fertility; in the latter case the children included many more of group O than would be expected if the survival of the zygote were unrelated to its blood-group.

J. A. FRASER ROBERTS (London, England) reviewed work on the associations of blood-group and disease, and presented new data. The original claims of an association of the ABO blood-groups with duodenal ulcers, gastric ulcers, and carcinoma of the stomach have been consistently confirmed in so many centres that their reality must be accepted. A distinct association on extensive data from one centre had been reported for tumours of the salivary glands, and this could to some extent be regarded as supporting the reality of associations of the ABO groups with carcinomas of the intervening œsophagus, and of the structurally similar pancreas. There was also suggestive evidence of an association with diabetes mellitus. Fraser Roberts drew particular attention to the inconsistencies between reports on other conditions from various centres. Some of these inconsistencies could hardly be fortuitous; and their interpretation, while probably more difficult, might be even more important than that of the clear-cut and consistent associations found in various disorders of the upper alimentary tract.

The Uterine Environment

A. MCLAREN and D. MICHIE (London, England) reported that on transplanting fertilised mouse ova into a foster-mother there was clear evidence that the number of lumbar vertebræ in the embryo tended to resemble that of the foster-mother more closely than that of either parent. The stage at which segmentation is determined excludes any simple mechanical or nutritional explanation.

K.-H. DEGENHARDT (Münster, Germany) demonstrated the consequences of exposing rabbits to an oxygen tension equivalent to that at 28,000 feet for four hours on the 9th day of pregnancy. A primary disturbance of the cell metabolism of the notochord predisposes to a generalised disturbance of the central nervous system and its surroundings somewhat similar to those found in anencephaly in man.

DOROTHY WARBURTON (Montreal) presented data on the factors influencing the spontaneous-abortion rate in man. The incidence in relation to a history of previous abortion varied smoothly between 14% in women who had not previously aborted and 26% in women who had had three previous spontaneous abortions. In relation to maternal age there was a smooth increase from an incidence of 12% in women under 25 years to 23% in women aged 40–44 years. A history of prematurity of previous infants appeared to be associated with an increased risk of abortion. Congenital deformities did not appear to be associated with a difference in incidence of abortion of other pregnancies, with the exception of cleft palate which was associated with a distinctly lower abortion-rate. No increased risk could be demonstrated in consanguineous marriages.

Familial Concentrations of Joint Disease

M. WHITTINGILL, E. H. HENDRICKS, G. S. TAYLOR, and L. S. THORPE (Chapel Hill, North Carolina) demonstrated a vast single pedigree involving 3000 persons with special reference to the distribution of rheumatoid arthritis, Still's disease, and spondylitis. Within the family as a whole the incidence of these diseases was comparable to that in the general population, but there was a definite several-fold increase in incidence in close relatives of affected persons. While relatives of cases of rheumatoid arthritis were particularly prone to rheumatoid arthritis, and relatives of cases of spondylitis were particularly prone to spondylitis, there was no tendency for relatives with one disease to be predisposed to the other. All fourteen cases of Still's disease were found in parts of the family unaffected by rheumatoid arthritis, and most were in close relatives of patients with spondylitis. Consanguinity also appeared to predispose to this disease. A remarkable but possibly fortuitous finding was that 14 cases of harelip were found, all in parts of the family unaffected by rheumatoid arthritis.

Detection of Carriers of Recessive Genes

D. Y-Y. HSAI, S. G. DRISCOLL, and E. M. S. GAWRONSKA (Chicago) discussed the advantages of being able to discriminate the heterozygous carriers of recessive genes. In phenylketonuria the estimation of the tyrosine-phenylalanine ratio allowed almost complete discrimination between these carriers and the normal heterozygote. In cystic fibrosis of the pancreas the sodium content of the sweat, although intermediate between that of the two homozygotes, was too variable to allow reliable discrimination. In the much rarer conditions of galactosæmia and von Gierke's disease evidence of impaired enzymic activity could be demonstrated in blood from most known heterozygotes, but this was not, at present, reliable as a method of discriminating carriers outside affected families.

H. HARRIS and E. B. ROBSON (London, England) presented extensive data on the families of patients with hypophosphatasia. Urinary chromotography showed that the majority of presumptive heterozygotes could be detected by their excretion of ethanolamine phosphate, while this metabolite could not be detected in a large series of controls. The proportion of heterozygotes excreting this varied greatly between different families.

Influence of Radiation in Man

H. J. MULLER and T. DOBZHANSKY, approaching the problems of the atomic age from their diverse theoretical standpoints, urgently drew attention to the future implications of diagnostic, industrial, and military irresponsibility—a theme later incorporated in a resolution by the congress as a whole. Muller's interpretation of the hazards to be anticipated is that

the general viability of the entire race will suffer, the main effect being on the vigour and longevity of adults. Dobzhansky, also arguing by analogies predominantly derived from the fruit-fly, sees no likelihood of any generalised impairment of health and bases his anxieties on the moral problem that the dissemination of atomic waste is largely in the hands of men who are prepared to expose the unborn to the unknown. There appears to be no informed doubt that the unborn have been, and will be, irretrievably exposed to the risks of recessively determined diseases on a scale previously associated with the execution rather than the preparation of war. While the numbers are large the proportions are so small that, even at the sites of the atomic bombs used in war, only in rice has unexceptionable evidence of unequivocal genetic change been demonstrated.

Medicine and the Law

Press Publicity before Trial

WHEN a criminal charge comes before the magistrates, it may be dealt with summarily: that is, the magistrates will decide whether the accused is guilty or not, and, if they find him guilty, decide upon sentence. In serious cases, however, the magistrates perform a different function. They decide whether there is a prima-facie case against the accused, and, if so, they commit him for trial before a jury at assizes or sessions. The magistrates have power to sit privately when doing this, but they nearly always sit in public, and the press can report the case fully.

Committal proceedings before the magistrates have not always been held in public. Before the days of organised police forces, the magistrates had the responsibility of arresting offenders; and, in deciding whether or not to commit for trial, they were also in effect performing a function now normally undertaken by the police—namely, deciding whether the accused should be charged at all. But, for the past hundred years or so, committal proceedings have nearly always been heard in public, and this has been felt to be in the best traditions of British justice.

There is a risk, however, that disclosures in the magistrates' court may prejudice the trial before the jury. Evidence may be brought before the magistrates, and widely reported, which is not in fact used at the trial. This happened in last year's trial of Dr. John Bodkin Adams. Before the magistrates, the prosecution led evidence of the circumstances in which two other patients had died; this evidence was not given at the trial. Moreover, there is some unfairness to the accused in that he may, quite properly, decide to reserve his defence—with the result that the press can report only the prosecution's case before the magistrates. Even if this does not attract such nation-wide publicity as that given to the Adams case and some others, a jury may be prejudiced by what they have read in a local paper.

After the Adams trial, the Lord Chancellor appointed a committee, with Lord Tucker as chairman, to consider possible remedies.[1] This committee is firmly against extending the number of hearings in private. It regards this as undesirable and unnecessary because the same end can be reached by restrictions on the right to report. The committee recommends that, unless the accused has been discharged, or until the trial is over, any report of committal proceedings should be limited to particulars of the name of the accused, the charge, the decision of the court, and similar facts. This recommendation cannot be put into practice without legislation.

1. Report of the Departmental Committee on Proceedings Before Examining Justices. Cmd. 479. H.M. Stationery Office, 1958.

In England Now

A Running Commentary by Peripatetic Correspondents

IN a little over two years I shall be 65, and Parliament has decreed that I shall be unfit by reason of age to treat patients in the Health Service and to teach medical students. I propose then to go to the bar, and "with a little bit of luck" I hope to become Lord Chief Justice in my early 70s. I may—but I make no promises—retire from that post when I am 81, but if I do I shall continue to sit as a judge in the Privy Council and the House of Lords, where, of course, I shall also help to make the laws—such as that one about consultants retiring at 65.

* * *

The path through Blossom Wood is vanishing. When we came, three years ago, it was not uncommon to see small parties of people wandering along it as it cut diagonally across the hanger beyond the stream at the foot of our garden. Sometimes they came from a picnicking car left where the path begins as a track higher up the lane: sometimes they were locals on a Sunday afternoon stroll or children lured by the bluebells in spring or the stately summer foxgloves. Last year there were fewer and now only a man with a gun is rarely seen.

Though it is a bridle-path marked on the official parish map, the farmer has wired up the far end to prevent his cattle straying into the wood, where one broke a leg recently—it is easier and cheaper than putting a stile or a gate. But the real reason for its rapid decay is Ted's purchase of a motor-bike on the never-never. Twice a day he used to walk along it to and from his work, and that was enough to keep it clear without conscious effort on anyone's part. Now the brambles spread across like thin green snakes, in places the bracken was shoulder-high this lush year, and in the little central groove where there used to be hoof-marks the young alders and birches are two feet tall and more. I have just spent a hard morning clearing my favourite part, from where the path from the ford in our garden joins it to the sunlit clearing where a great spotted woodpecker often clings in his uniform of black, white, and red like the Kaiser's flag. But I know it's a hopeless battle since Ted got his motor-bike.

* * *

AS we had been given the tickets, my wife and I were determined to visit the flower show. I hurried through my morning clinic and we set off. Our enthusiasm was slightly damped by the half-mile walk from the car park, the crowds of people, and the sultry, thundery weather. However, we went straight to the Grand Marquee for Non-competitive Trade Entries and forced ourselves towards the Rose Display by the well-known technique of accusing mythical people behind you of pushing you rudely forwards. Hardly had I arrived at my goal and begun to write down the names of next year's purchases when the loud-speaker stopped its "No smoking" requests and said, "Will any doctor in the grand marquee please go to the ambulance tent at once." Reluctantly and with even greater difficulty I forced my way out, and, asking my wife to wait at the marquee entrance, went to the ambulance tent.

A very large and elderly lady had collapsed with substernal pain. She said that she was subject to heart attacks for which she took tablets, but that, as she had wanted a day off, a really good outing, and a complete change, she had left the tablets at home. The St. John Ambulance Brigade and I undid her corsets and I applied my ear to the lower part of her sternum. Both heart and bowel sounds were loud, clear, regular, and unhurried. I straightened my back and considered the next step. At this critical moment, to my relief, another, obviously professional, figure entered the tent. "Ah, a proper doctor, I see," I said, "I am only an orthopædic surgeon; I am sure this lady will receive better advice from you than from me." "I am sorry, I am only a medical officer of health," was the answer. We consulted together and decided that the interests of the majority of those present in the tent would be served

best if she was taken by ambulance to the casualty department of the local infirmary.

Needless to say, my wife was no longer at the marquee entrance. When we did meet, some time later, it was obviously hopeless to try to enter any of the marquees, so we consoled ourselves with the sundries section. By the time I had bought several garden chairs, tables, and other horticultural aids I realised that it had been an expensive consultation.

• • •

In these days of highly specialised anæsthesia when it is so easy to attribute difficulty to some misbehaviour of the flowmeter or to some atypical activity at the end-plates, it is strange to look back to the days when the man dozing at the head of the table took some responsibility for things going wrong. I shall always look back with pleasure to the day when I worked with a Hibernian anæsthetist who had all the charm of his race. If I said "is there a little congestion?", he would promptly reply "Yes, indade, she's absolutely purrrple". Or if I asked "Is she straining a little?", he would reply "Yes, she's as harrd as a boarrd".

• • •

Seated one day at the Dog Show, I was weary and ill at ease until I overheard two ladies discussing their doctors. In readiness for the day when such doctor-fanciers hold doctor-shows at which they will walk their favourite practitioners round in a large circle—instead of, as at present, running them round in small ones—I offer a basic classification of the zoological genus *Medicus*.

1. *M. hocuspocus* (or Quackshund)—a common wild (non-registered) species, developed from Barbary corsair blood-lines.

2. *M. familiaris*—a well-broken species including such types as *M. geepee debilitatus* (Bevan) or *M. spina professionis*, according to who's talking. This type belongs to the great working group of *Medicus* and is of great utilitarian value, being used as draught animals, distributors of susstificates, herders of livestock (which are rounded up with great alacrity), and guide-animals for the socially inadequate. *M. geepee deb.* (Bevan) hunts singly or in small packs, ranging rapidly about a terrain which it most jealously preserves.

Good points are long pendulous ears (for meshing with stethoscopes), powerful and free-acting hind legs, long memories, thick skins, and poor appetites. Attempts to deepen the purse of this type have been unsuccessful. Coats range from hairless to long-haired varieties. Common colours are white, livery, puce-magenta, grey grizzled, and tartan. These animals prefer fur-bearing well-heeled prey and have the temperament, size, and intelligence to qualify as household pets.

Individual breeds of *M. familiaris* include *M. chirurgus*, a sporting type from retriever blood-lines, pursuing fur- (mink for choice) bearing prey which it flushes out very thoroughly. *M. chirurgus* works best in excavations, orifices, and cavities. Usual colours are white, white mask with rufous muzzle, prominent abdomen, and alert expression. For these animals to kill prey is a disadvantage . . .

And now if you fellow dogsbodies will excuse me I have to see a patient about a condition powder.

• • •

"They fool me to the top of my bent". Thus, with Hamlet, must be thinking the ghost of the illustrious Emile Coudé. His grandnephew, M. Hercule Coudé, has done us service in keeping his name to the fore; but, alas, he falls into the popular error of attributing the straight catheter to M. Jaques.

It is natural to associate catheters with the French, but in this case the catheter is English. Its date of origin is unknown, but it was widely used in the 18th century when, for obvious reasons, it was known simply as "the jakes". In the Victorian era feelings against the name ran high, and it was impossible to move in urological circles without becoming involved in heated arguments. The climax was reached at a certain meeting when it was decided to consign the jakes to oblivion. This so affected a French visitor that he leapt to his feet with the now famous ejaculation: "Eurethra!" Called to the rostrum, this man, M. Jaques, gave an impassioned speech in which he implored the audience to consider the patient before any matter of prudery. He saved the day, and since then the spelling of the catheter has been "Jaques".

Letters to the Editor

CHILDREN IN HOSPITAL

SIR,—If a child is suddenly whisked away from home with, say, acute appendicitis, daily visiting is undoubtedly a great advantage. The patient is likely to be ill and in pain and everything happens too quickly for him to be able to adjust himself. Not so in a long-term hospital. Here the patient's stay is of many weeks or months; he has time to reorientate himself and learns to make the hospital his temporary home. Patients in such hospitals are always drawn from a wide area and visiting is expensive both in time and in money.

Because the patients are usually well and because they are in hospital a long time, orthopædic hospitals have always been cheerful and rather unconventional places. At this hospital there are school lessons and cinema shows, birthday teas on the lawn, and a Boy Scout troop; and the child feels that he is a member of a community much, I suppose, as a child who has been sent to boarding school.

All this has been pointed out before, and in a number of long-stay hospitals with whom I have been in touch the introduction of frequent visiting has been resisted by the senior staff. Yet, because of the propaganda by psychiatrists and psychiatrically minded pædiatricians, the Ministry of Health has more or less forced us to increase visiting from one to three days per week, and pressure is now being exerted to introduce daily visiting.

This propaganda is being backed up by a film *A Two-year-old Goes to Hospital*. I am unimpressed by it as a serious argument in a serious discussion. Ever since the days of Al Jolson, audiences have been moved to tears by the pathetic appearance of a small child looking sadly through the bars of a cot. Only then, if I remember rightly, the child was looking accusingly not at an ogre of a Matron but at Daddy who was not visiting Sonny Boy any longer because he and Mummy could not get on together. . . . Let me be careful in what I say. If on the day of admission and under the immediate impact of the separation we asked our mothers whether they wanted daily visiting or not, a number would probably opt for it. But soon they find to their amazement that the children are settling down perfectly well. It is a tragedy to develop a tuberculous hip, but, properly handled, even a boy of five can adjust himself to such a situation, can understand that he is in hospital because he has a poorly leg and that his mother will visit him on Sunday. Again, let me admit that there are exceptions and it is the child of 18 months or so who is most likely to find difficulties. This is the awkward age when one is old enough to worry about one's surroundings but not quite old enough to understand. Recently we had such a little girl in with poliomyelitis; she settled badly, was bewildered and withdrawn. Because she was difficult I arranged for the mother to call in every day, to go with the child to the massage department, to sit by the bed side when I did my ward rounds. The response was good, and when the mother called on me a fortnight later we agreed that things had improved a good deal. The question she then asked me was typical. Not "I hope you will nevertheless not withdraw the privilege of daily visiting", but "do I still have to come every day?"

When the three visiting days per week were introduced at this hospital I wrote a circular letter to the parents which was handed out on a certain Sunday afternoon at 2 o'clock. At 2.10 there was a knock at the office door and one of the sisters asked me to come to her ward. "There is almost a riot on, Sir" was the report. I went and found myself surrounded by mothers who wanted to know what "all this is about." They asked when were they to do their shopping? Who, they wondered, was going to get the tea ready for their husbands coming home from work? I told them that this was only a

permission to visit, that they did not *have* to come every time if they were busy; but they looked through that argument at once. If there was no visiting, they said, their child would not miss them, but if there was he would feel neglected unless they came. And so they come, or arrange for Granny to come, and even pay neighbours to visit their child so that he should not feel neglected on visiting day. Travelling as much as three hours here, and three hours back, summer and winter, for months and months.

However this question goes further. It has been said by psychiatrists that the separation of a child from his mother causes severe, lasting psychological damage. That there is a direct connection between it and such things as juvenile delinquency; and long-stay orthopædic hospitals have been singled out for blame in this matter. This is not our experience at all. Orthopædic surgeons who work with these crippled children find that they grow up into perfectly well adjusted adults and good citizens. In the ordinary run of fracture-clinic patients they stand out because of their quiet, non-complaining behaviour. Far from being bitter their suffering has made them considerate of others. Dare one suggest that sometimes difficulties, properly met, ennoble the character?

Permit me, Sir, to end with a letter I received a few days ago from a farmer's wife in Derbyshire. It concerns a boy of 6 who had poliomyelitis and who is to come into hospital for an operation:

> "Dear Doctor, I am sorry to say John's sister broke out in German Measles today, there is only John who has not had them now. So all being well I will write again on the 26th of August and let you know how things are. John is very disappointed he is unable to come to the hospital yet, as he is looking forward to coming very much. I, John's mother, had German Measles three weeks ago. Yours truly. Mrs. X."

King Edward VII Orthopædic Hospital, Sheffield. E. G. HERZOG.

SIR,—Professor Illingworth's thoughtful lecture (July 26) and your own forthright leading article have evoked replies which by their vehemence cloud the main issues and exaggerate the minor ones.

No one will deny that the larger infectious-diseases hospitals situated in and serving a heavily populated area provide an essential and efficient infectious-diseases service.

A different picture is presented by many of the smaller infectious-diseases hospitals, some of which do not have a resident medical officer, and where clinical-laboratory and radiological facilities are absent or rudimentary. Admissions are sometimes accepted by nursing staff or even clerks. The term "infectious" is interpreted in its widest sense. A consultant in infectious diseases, at his main hospital 15–20 miles away, cannot hope to provide adequate supervision of urgent cases.

A clinical laboratory is as essential in the treatment of meningitis as an operating-theatre is in the treatment of acute appendicitis. No-one would consider admitting a case of appendicitis to a hospital without a theatre constantly staffed. Cases of meningitis are admitted to these small infectious-diseases hospitals with little or no laboratory facilities.

The Ministry's approach to this important matter is difficult to understand. They have suggested, and it is widely accepted, that infectious blocks should be included within the curtilage of all new general hospitals. The present central infectious hospitals would, of course, continue to provide for local needs and for cases from further afield which, because of their complexity or epidemiological character, require the specialised skill and equipment only available at such hospitals. It comes, therefore, as a surprise to learn that the plans for the new Huddersfield General Hospital of 600 beds, one of the first in the country, do not provide for an infectious block. This would seem to be a retrograde step, more especially as it may create a precedent.

Dr. Breen (Aug. 16) is seriously misinformed when he states that pædiatricians "have wrought so well as to imperil their own survival". He presumably bases this statement on the prevalent misconception that the amount of work done in a specialty depends on the number of beds allocated. A careful analysis of the figures will show, broadly speaking, that in those areas where the number of pædiatric beds has fallen by a half over the past five to ten years, the number of outpatients have practically doubled. It is generally accepted that outpatients are by far the most responsible and onerous part of a physician's work, a burden that the infectious-diseases consultant is very largely spared. New pædiatric appointments are being made and old appointments split. It is noteworthy that between 1934 and 1956 in the U.S.A. the number of pædiatricians has quadrupled, while in the same time the total of physicians has increased by only a third. Such an increase is exceptional, but the trend is obvious in other countries as well.

Halifax General Hospital. W. P. SWEETNAM.

SIR,—Professor Illingworth's lecture and your leading article raise a number of points involving fever hospitals.

These hospitals have long since discontinued routine admission of uncomplicated scarlet fever and measles. On the other hand, pneumonia is a notifiable infectious disease, while "meningitis" may include a variety of conditions, some notifiable such as cerebrospinal fever and, sometimes, poliomyelitis. It is therefore both logical and safer to send these cases to fever hospitals, whose senior consultants, incidentally, have an unrivalled experience of these infections—not to mention gastroenteritis.

Professor Illingworth decries the efficacy of cubicles in the prevention of cross-infection, and while this may in some instances be true—gastroenteritis due to *Escherichia coli*, for example—the successful segregation of all types of infectious diseases alongside each other has been carried out for years in fever hospitals. The reason for trouble in other types of hospital, even with cubicles, may well be failure to apply efficiently the approved techniques of fever nursing—a potent argument for the retention of this particular training.

Undoubtedly, many pædiatricians have had extensive experience of infectious diseases, but this can hardly be universal. There is surely some arrogance in claims that the age of the patient rather than the physician's experience of the diseases concerned should determine who is to look after him. If pædiatricians are so anxious to assume control of infectious diseases, they should at least make it compulsory for their trainees to serve an apprenticeship, preferably as residents in fever hospitals.

An alternative solution for the main fever hospitals, which had the blessing of the Royal College of Physicians, is that they should be run by general physicians with a primary interest in infectious diseases. This is in practice very frequently the case, in fact if not in name. Surplus beds, if any, can then more easily be devoted to general medicine rather than pædiatrics, and staffed where necessary with the help of outside consultants. These beds could readily be switched back to fevers in the event of an epidemic. The continuity of medical administration, inseparable from fever practice, still intimately linked with the public-health service and based on long experience, would be preserved. The disruption of attached special units, such as

those for poliomyelitis or tuberculous meningitis, into separate age-categories, a process wasteful of medical experience and efficiency, as well as of physical resources and money, would be avoided.

Have the pædiatricians given due thought to the public-health aspects of the case, and to what medical officers of health think?

Hoylake, Cheshire. J. L. FLUKER.

SIR,—Since the publication of Dr. Lawson's letter (Aug. 23), I have heard from Mr. A. G. Linfield, chairman of the South West Metropolitan Regional Hospital Board, and I gladly accept his assurance that it was not his intention, at the interview which we had, together with Major-General Hawes, on July 23, to convey to me the impression that the board were in any way committed by the Ministry's suggestion to close Queen Mary's as a general children's hospital.

Queen Mary's Hospital for Children, Carshalton, Surrey. H. J. WELLS Chairman of Management Committee.

APPROVED NAMES

SIR,—The interim report of the Committee on Cost of Prescribing contains various criticisms of the approved names which the General Medical Council publishes on the advice of the British Pharmacopœia Commission. The commission was not advised by the committee that it proposed to discuss approved names; but had this intention been known the commission would have wished to furnish evidence for the committee's information, thereby avoiding the many inaccuracies which appear in the report. The commission regrets that they were not invited to appear before the committee.

The commission now offers the following observations on some of the statements which appear in the report.

1. The report states (para. 41): "There are for example just under 5000 proprietary preparations available for prescribing. Economies would follow, we believe, if simple approved names for new products could be evolved quickly and given the widest possible publicity."

In the majority of cases the provision of an approved name has no effect on the price of preparations. The issue of the simple approved name primidone for the product 'Mysoline' has had no effect on the price of the drug—to quote only one of numerous possible examples.

2. The committee states in para. 42 of the report that "We are informed, for example, that the present rules of nomenclature require that the approved name should be based on a drug's chemical constitution."

This statement is erroneous. The guiding principles used in selecting or devising approved names do not impose an inflexible style and it will be seen that many names are not based on the drug's chemical constitution—e.g., most antibiotics, warfarin, azovan blue, gallamine, lignocaine, macrogol, mustine, sulphan blue. Among these guiding principles are the following:

"An attempt should first be made to form a name by the combination of letters or syllables from the systematic chemical name.

Cognisance should be taken of the names of closely related substances and where desirable the name should reflect this relationship.

The names should be distinctive in sound and spelling and should not be liable to confusion with names already in use.

Names which are difficult to pronounce or remember should be avoided.

Names used in the *United States Pharmacopœia, New and Nonofficial Remedies* (Drugs), and international non-proprietary names should receive preferential consideration."

In giving preferential consideration to existing non-proprietary names, and so avoiding the international confusion which may arise if a second name is adopted for the same drug, the commission has found it preferable in some instances to accept such a name in spite of its defects. For example, the names chlorotrianisene, diphenylpyraline, and tripelennamine were issued by the American Medical Association and widely used before the drugs were sold in Britain. Although the commission was critical of these names, the balance of advantage lay in accepting them as approved names.

3. The report states (para. 43) that "At present a year or two may elapse before an approved name is formulated for a new drug. During this period doctors get into the habit of prescribing the new preparations by their trade names . . .".

It is exceptional for a long period to elapse between the appearance of a new drug on the English market and the publication of an approved name. Approved names for new drugs of English origin are usually available by the time the drug is placed on sale and indeed the approved name is generally available before the drug is distributed.

During the past five years, nearly 60,000 copies of lists of approved names have been circulated by the commission, but wide advertisement is the most potent factor in establishing the names of medicinal products and it is manifestly not a function of the commission to advertise approved names in the manner or on the scale adopted for trade names. Copies of supplementary lists of approved names are supplied to some hundreds of correspondents at home and abroad and they are published in many professional journals.

4. The committee states in para. 46 of its report that "We consider also that before putting a new drug on the market manufacturers should be encouraged to ask the British Pharmacopœia Commission to give it an approved name. As soon as that has been done. the approved name should appear on labels and advertising literature for proprietary preparations as prominently as the trade one".

Over many years it has been the practice of most British manufacturers to approach the commission for an approved name for a new drug before placing it on the market. For such products the approved name is usually available whilst the substance is undergoing trials and before it is generally released for sale. The commission has no control over the manner in which approved names are used by manufacturers on labels and in advertising literature.

5. The committee expresses the opinion (para. 44) that "some of the principles of nomenclature now in force may well be inappropriate today", and recommends that the commission be asked to review these principles. It is difficult to comply with this request unless a more specific statement is provided.

The report makes no reference to a number of important considerations that apply in the selection of approved names, such as the international aspects including the non-proprietary names issued by the World Health Organisation, and by the American Medical Association for many drugs that appear in England only after a period of use in the United States. Indeed most drugs introduced on the English market have had a period of use in the United States or elsewhere in association with a non-proprietary name, and unless over-riding considerations apply it is undesirable to coin a second non-proprietary name even when the established name falls short of the commission's desideratum. Approved names are applied not only, and perhaps not primarily, in the writing of prescriptions but also in scientific articles appearing in journals with world-wide readership, for reference purposes, and in the labelling of products in accordance with legal requirements including purchase-tax and poisons regulations. Approved names are also of great value in indicating to prescribers and pharmacists that the same drug is being described under more than one trade name.

Attention is also drawn to the problems which arise in relation to existing names especially those registered as trade marks. It has been a frequent experience that a proposal for what would appear to be an admirable short name must be discarded in favour of a more complicated one because, on the authoritative advice received by the commission from the Patent Office, the short name is held to conflict with a trade mark registered in this country.

The commission offers this statement in the hope that it may dispel any misunderstanding which the report may have created, and that it may help towards a better appreciation of the origins and purposes of approved names.

D. M. DUNLOP
Chairman, British Pharmacopœia Commission 1953-1958.

General Medical Council Office, 44, Hallam Street, London, W.1.

T. C. DENSTON
Secretary.

MIDGET ANÆSTHETIC MACHINES

SIR,—In your annotation of Aug. 16 you draw attention to the development of two midget anæsthetic machines which depend on a non-explosive cyclopropane mixture to give but a few minutes' anæsthesia.

I have long felt that there might be a place for a really portable apparatus capable of producing anæsthesia of one to two hours' duration, for possible use in the Services, major disasters, industrial accidents, shipping and air lines, &c., and with this end in view I have adapted an existing lightweight oxygen therapy unit into a halothane/oxygen closed-circuit anæsthetic machine with various refillable or "throw-away" components. This apparatus is still in process of manufacture, testing, and calibration.

Southlands Hospital, Shoreham-by-Sea.

P. J. C. BURTON.

ANATOMY OF THE CARDIA

SIR,—Some of the conclusions endorsed in your leading article of Aug. 16 are still controversial.

In particular, the opinion of Atkinson et al.[1] that a raised pressure zone in the lower œsophagus immediately above a hiatus hernia signifies the activity of a "sphincteric barrier" is open to criticism. Jennings [2] in his review of this paper has already pointed out that in such cases the recording tube, as a foreign body, might well cause sustained contractions of the lower œsophagus.

Undoubtedly the œsophagus immediately above the œsophagogastric junction exhibits particular properties of distensibility and contraction, sufficient to be designated the "gastroœsophageal segment of expulsion" by Lerche,[3] but this does not necessarily imply that it serves to prevent reflux. It may chiefly be concerned with forward propulsion after swallowing, by contraction of the segment as a whole, analogous to the distal pyloric antrum.

Several investigators have mentioned the apparent weakness of this "pressure barrier".[4–6] Wolf et al. believe that the terminal œsophageal segment is so easily ballooned out that it constitutes part of the hernial pouch, the junction appearing in cineradiographs as a shallow horizontal groove. Actual invagination of the distal œsophagus in hiatus hernia has been reported by Kleinfelter.[7]

The area from which Atkinson et al.'s pressure recordings were taken, therefore, may have been the distal 1–3 cm. of the "tubular" œsophagus and not the most distal segment. In radiographs this former region often appears narrowed for several centimetres, and it may be more irritable than normal because of œsophagitis.

The observation that delay in passage of barium through the œsophagogastric junction can be abolished by continuous drinking of barium, as distinct from individual swallows, does not prove that they are different physiological processes, as Creamer and Pierce would have us believe. The build-up of pressure by rapid passage of a heavy liquid such as barium might be sufficient to obliterate this weak "sphincter" zone.

In spite of the inability of Atkinson et al. to demonstrate a change of pressure where the hernial neck passes through the hiatus, the fact remains that in a large proportion of cases the radiologist is unable to fill the hernia by reflux from the stomach. (Flood and Hennig,[8] for example, report reflux in 31 out of 70 cases, many having repeated examinations.) Wolf et al. observe that the site at which reflux is most often obstructed is at the level of the hiatus—i.e., the mechanism is extrinsic. Presumably this functions effectively during the examination and at other times; but at night, particularly when a low tone in the crus combines with the supine position, reflex occurs.

In my limited radiological experience I have found no correlation between the presence or absence of reflux symptoms and the extent to which radiological reflux takes place—i.e., whether only the hernial pouch is filled or the whole œsophagus.

Southmead Hospital, Westbury-on-Trym, Bristol.

E. A. W. HOUGHTON.

HÆMOPHILIA-LIKE STATES IN GIRLS

SIR,—Dr. C. Merskey (Aug. 2) has commented on the omission in our paper [9] of the family first reported by Treves [10] in 1886 and re-studied by him in 1950.[11] This family was not discussed because of the atypical hereditary pattern.

In the first four generations the disease was reported to have been transmitted from father to son, which does not occur in classical hæmophilia. We, of course, cannot judge the validity of these early reports. We were impressed by the apparent severity of the bleeding state in the members of this family, despite the fact that their clotting-times were only slightly prolonged. In both true hæmophilia and Christmas disease, it is uncommon to find permanent ankylosis of joints in patients whose clotting-times are only one or two minutes above normal.

The unequivocal diagnosis of classical hæmophilia can only be made if the typical hereditary pattern is obtainable, if the bleeding and prothrombin times are normal, and if the absence of the specific factor, thromboplastinogen (antihæmophilic globulin), can be established with certainty. The coagulation defect of the girl we reported is, according to all the tests now available, identical with that of true hæmophilia; nevertheless, the diagnosis of classical hæmophilia cannot be made because of the absence of a hereditary history. The bleeding condition in one of a pair of identical twins which Dr. Conway and I reported [12] also corresponded closely to classical hæmophilia, but again the diagnosis could not be made with certainty because of the atypical hereditary pattern.

The question arises as to what determines the basis for applying the term "hæmophilia". If it is the characteristic hereditary pattern, then Christmas disease or P.T.C. deficiency can justifiably be called hæmophilia B. If,

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4. Adler, H., Ferme, C. N., Lanigan, J. M. *Surgery*, 1958, **44**, 63.
5. Creamer, B., Pierce, J. W. *Lancet*, 1957, ii, 1307.
6. Wolf, B. S., Marshak, R. H., Som, M. L., Brahms. S. A., Greenberg, E. I. *J. Mt Sinai Hosp.* 1958, **2**, 167.
7. Kleinfelter, E. *Radiology*, 1956, **57**, 562.
8. Flood, C. A., Hennig, G. C. *Gastroenterology*, 1958, **35**, 62.
9. Quick, A. J., Hussey, C. V. *Lancet*, 1958, i, 1294.
10. Treves, F. *ibid.* 1886, ii, 533.
11. Merskey, C. *Quart. J. Med.* 1950, **20**, 299.
12. Quick, A. J., Conway, J. P. *Amer. J. Med.* 1949, **7**, 841.

however, it is the lack of thromboplastinogen which determines the name, the term hæmophilia B is illogical, but angiohæmophilia or vascular hæmophilia would be a suitable name for the disease in which the thromboplastinogen is deficient and the bleeding-time is prolonged. Pseudohæmophilia would be the preferred name, however, if hæmophilia designates the hereditary pattern.

Marquette University School of Medicine, Milwaukee, Wisconsin. ARMAND J. QUICK.

COUDÉ STRAIGHTENED OUT

SIR,—As the author of the article on Coudé mentioned by Mr. Hamilton Bailey and others (Aug. 23), I feel that to call the article a "deception" or "hoax" is unfair. None of the Cardiff students did anything to bring the article to the attention of anyone connected with *A Short Practice of Surgery*. Coudé is something of a standing joke in Cardiff, and nobody really believed in him.

I have not yet given up all hope of revising our knowledge of medical history. I am now doing some research about Pyogenes, an Ancient Greek who postulated the existence of the staphylococcus many years before the microscope was invented. I hope that before long he will achieve his fair share of fame, in the form of a footnote in our most popular textbook on bacteriology.

Morriston Hospital, Swansea. RAPHAEL PASH.

THE WAALER-ROSE FACTOR IN RHEUMATOID ARTHRITIS

SIR,—I have not been able to satisfy myself that my arthritic patients will be helped by the knowledge that their serum may potentiate the agglutination of sheep cells sensitised with rabbit amboceptor.[1] I shall comfort myself with the words of Broussais [2]: "Facts which cannot be used for healing do not belong to the physician; they belong to the naturalist." This test is based on the gospel that rheumatoid arthritis is an entity, separate and distinct from all other diseases. But Clifford Allbutt [3] said in 1866: "We are now but awakening from the metaphysical delusion that diseases are separate entities." Poynton [4] wrote of the rheumatic disorders as "allied disorders [with] strange likenesses as well as strange differences. For the student it is easier and more helpful to define differences, but for the expert it is often of service to study similarities".

In our present state of ignorance of its causation, such terms as rheumatoid arthritis can only be tentative. A word like "rheumatoid" can be used as we use "carcinoma" to signify a real change in the tissues. Then it must be applicable to monoarthritis and the infective forms of arthritis as well as to polyarthritis. Or we can use rheumatoid in its popular sense, as a convenient term like scrofula and dropsy. It is purely tentative and at the next advance in knowledge may be swept away. At present there is a danger that knowledge be suppressed by insisting too much on a "diagnosis" as the basis for the discussion of any rheumatic patient's symptoms.

Not one of the fifty or so extant classifications of rheumatism can include more than 60% of all cases.[5 6] Cobb [7] was unable to fit more than one-eighth of 372 rheumatic patients comfortably into any of the standard categories. Mainland [8] has also shown how unworkable are all attempts to classify rheumatism.

Much of the present confusion in rheumatology is due to superstitious belief in the ancient terms, acute and chronic, and has arisen because our desire to classify has outrun our knowledge. If we are guided by superficial appearances only, we shall be like the two boys who were asked to grade a sack of apples. Not knowing that there existed real differences between the apples (Rome Beauties, Jonathans, &c.), one graded his half into large apples and small apples, while the other also had two heaps, red apples and green apples. Needless to say, in both lots there were many intermediate and unclassifiable types.

Melbourne. MICHAEL KELLY.

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3. Rolleston, H. D. Life of Sir Clifford Allbutt. London, 1929.
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6. Robinson, W. D., et al. *Ann. intern. Med.* 1953, **39**, 497.
7. Cobb, S., Merchant, W. R., Warren, J. E. *J. chron. Dis.* 1955, **2**, 50.
8. Mainland, D. *Ann. rheum. Dis.* 1955, **14**, 337.

SHOULD BIBLIOGRAPHIES GIVE TITLES OF PAPERS?

SIR,—Dr. Max Millard (Aug. 16) suggests that *The Lancet* make the gesture—how he cannot suggest. May I propose this gesture which would help and cost little extra space: adding the concluding page of all articles quoted?

Wyke House Hospital, Isleworth, Middlesex. H. PULLAR-STRECKER.

TOBACCO AMBLYOPIA

SIR,—The interesting article by Dr. Heaton and his colleagues in your issue of Aug. 9 mentions the low serum-vitamin-B_{12} levels in vegans, who, because they consume no animal food, tend to develop a dietary deficiency of vitamin B_{12} and therefore may provide valuable information on this subject.

My colleagues and I in our investigations on vegan non-smokers have found their low serum-B_{12} levels to be associated with an increased urinary excretion of thiocyanate [1] which could be reduced by oral or parenteral administration of vitamin B_{12}.[2] In a communication [3] to the Fourth International Congress of Biochemistry in Vienna, we propose to show that in non-vegan smokers there is also an increase in the urinary excretion of thiocyanate roughly proportional to the degree of smoking and parallel with the increase in serum-thiocyanate recently found by Stoa [4] in smokers. This increase in thiocyanate excretion may occur also in "stress" conditions such as menstruation, pregnancy, or lactation when there is an increased requirement for vitamin B_{12}. It may have a bearing on the suggestion of Heaton et al. that the beneficial effects of vitamin B_{12} on tobacco amblyopia are due to its making good a deficient intake of the vitamin. Vegans who are subject to such a deficiency are usually non-smokers. However "eye trouble", which is now being investigated, has been encountered in a life vegetarian (living on an almost vegan diet) after she had voluntarily taken up extensive smoking for some time, and greatly increased her urinary excretion of thiocyanate.

Thiocyanate is formed in the body by the action of the liver enzyme rhodanese on cyanide.[5] After administration of ^{14}C-labelled cyanide to dogs most of the radioactivity has appeared as $S^{14}CN$ in the urine.[6] It therefore seems logical to assume that an increase in thiocyanate excretion during smoking would be caused by any cyanide derived from the tobacco. Tobacco smoke has been shown to contain cyanide in amounts of the order to be expected if the increase of 5–20 mg. in the daily thiocyanate excretion in smokers were due to cyanide inhaled in the tobacco smoke.[7]

These findings indicate that it would be of interest to study the cyanide and thiocyanate metabolism in tobacco amblyopia.

1. Wokes, F., Badenoch, J., Sinclair, H. M. *Voeding*, 1955, **16**, 590; *Amer. J. clin. Nutr.* 1955, **3**, 375.
2. Wokes, F., Picard, C. W., Paper read to Third International Congress of Biochemistry, Brussels, 1955.
3. Wokes, F., Hytten, F. Paper to be read to Fourth International Congress of Biochemistry, Vienna, 1958.
4. Stoa, K. F. Studies on Thiocyanate in Serum. University of Bergen, 1957.
5. Lang, K. *Biochem. Z.* 1933, **262**, 14.
6. Boxer, G. E., Rickards, J. C. *Arch. Biochem. Biophys.* 1952, **39**, 7.
7. Osborne, J. S., Adamek, S., Hobbs, M. E. *Anal. Chem.* 1956, **28**, 211.

There might be expected to be a high rate of urinary excretion of thiocyanate, which would be decreased by administration of vitamin B_{12}, and the rate of decrease might perhaps be compared with the clinical improvement as measured, for example, by visual acuity. Should this occur, a useful biochemical method might emerge of studying the development and treatment of this disease.

The action of the vitamin may be better understood if it be pictured as existing in the body largely in the form of hydroxocobalamin, which can absorb cyanide very readily to form cyanocobalamin. The latter could then take part in essential metabolic processes involving the use of cyanide as a brake on respiratory enzymes such as cytochrome oxidase. Based on these theories, a hypothesis [8] has been put forward regarding a possible role of vitamin B_{12} in human nutrition, involving its participation in the synthesis of methionine. This is one of the sulphur-containing aminoacids in the lens of the eye in which main interest has long been centred.[9] In the metabolism of the lens cytochrome oxidase, which plays an important part, is inhibited by cyanide, which may function as a necessary brake on the activity of the enzyme and thus be indeed an essential metabolite. The rate of excretion of minute traces of cyanide in the breath of normal subjects has been found to be related to the basal metabolism, indicating that the cyanide is taking part in general metabolic processes.[10]

These theoretical aspects may provide a basis for the practical treatment or prevention of tobacco amblyopia by administration of vitamin B_{12}, preferably orally, in frequent small doses, supplemented perhaps with thiamine and other B vitamins. Study of the cyanide-thiocyanate metabolism (e.g., by estimation of serum-thiocyanate or of urinary thiocyanate excretion) might be helpful.

King's Langley, Herts. FRANK WOKES.

SIR,—I was very interested in the article by Dr. Heaton and his colleagues. I should like to comment on the suggestion that the nutritional retrobulbar neuritis of prisoners of war may be due to a combined deficiency of vitamins B_1 and B_{12}.

In West Africa, some of my most extended trials were done with autoclaved 'Marmite'. This was a follow-up of the work of Landor and Pallister [11] at Changi Civil Prison, Malaya, who had demonstrated that autoclaved marmite would cure the skin lesions of what is recognised today as "ariboflavinosis", as would ordinary marmite, which I had been using. There was also strong presumptive evidence of a similar effect on vision.

While autoclaved marmite produced dramatic cures of the more visible lesions, including keratitis, confirmative evidence about neurological lesions required months of observation and careful selection of cases. Only those with a very recent history of nutritional retrobulbar neuritis could be selected, for within a few months irreversible changes would occur and a known effective treatment could not be long withheld. I found nutritional retrobulbar neuritis responded as well to autoclaved marmite as ordinary marmite.

Beriberi was a rare disease in Southern Nigeria where the staple carbohydrates were different from the Far East, and rice a "luxury". I saw no evidence of it, clinically, in any patient.

The discovery of ariboflavinosis cleared any doubts about the oral and skin lesions, formerly held to be "pellagrous" (though by 1938 nicotinic acid had been virtually excluded). But any coexistent neurological condition remained obscure. My own belief is that marmite contains that "something else", still unknown, which is both a protective and curative factor. Against riboflavine affecting neurological conditions is the absence of experimental proof. As long ago as 1940 V. P. Sydenstricker told me that neither he nor his colleagues had been able to find any evidence of retrobulbar neuritis in their cases of ariboflavinosis.

Vitamin B_{12} has always offered a possible link-up with these problems and has been a logical consideration for follow-up ever since its discovery. So far as I know the only such trial has been that of J. H. Walters in Arabia. In a personal communication (1953) he informed me of its success in cases of recent origin of a nutritional ataxic syndrome. This condition however, appeared to be separate from nutritional retrobulbar neuritis as in none of his cases was there any evidence of this.

It may well be there is more than one type of dietetically produced "cord" syndrome. Pallister [12] described an ataxic paraplegia in Chinese Malays which was not associated with a retrobulbar neuritis.

Finally, almost all P.O.W./F.E. medical officers state that nutritional retrobulbar neuritis is not caused by vitamin B_1 deficiency. Denny-Brown [13] and Spillane,[14] both of whom conducted exhaustive surveys of nutritional neurological conditions in Service personnel, said the same.

Nutritional retrobulbar neuritis is a true deficiency disease. While much can be definitely excluded, its exact cause remains unknown.

Parkstone, Dorset. D. FITZGERALD MOORE.

LECTURES ON TAPE

SIR,—We read with interest Dr. Oakley's letter (Aug. 23) in which he mentions our suggestions for a library of medical tape-recordings. He, and others, may like to know that, although our original ideas have been greatly modified, they have developed into the Medical Recording Service of the College of General Practitioners, which has for some months now been issuing talks on tape and long-play gramophone records to members of the College.

Chelmsford, Essex. JOHN GRAVES
VALERIE GRAVES.

TREATMENT OF NEPHROTIC SYNDROME WITH CHLOROQUINE

SIR,—The usefulness of adrenal corticoid therapy in treatment of the nephrotic syndrome is well documented and has been recently reviewed.[15] Dr. M. Plaza de los Reyes (July 19) reports good results following the administration of 0·75 to 1·0 g. chloroquine diphosphate for 2 to 4 months to three patients with "the nephrotic type of chronic nephritis". Our own experience with chloroquine therapy in three adults and four children with idiopathic nephrotic syndrome has been disappointing.

The children received at least 0·25 g. and the adults 0·75 g. chloroquine diphosphate for 2–3 weeks. The hydroxy-ethyl amino analogue of chloroquine was administered to two children. A complete remission occurred in one child and proteinuria decreased in two adults. However, no improvement occurred in the other four patients, although subsequent corticoid therapy produced complete remission (disappearance of proteinuria) in all of them. Thus, in our experience with somewhat smaller dosage and shorter courses than those employed by Dr. Plaza de los Reyes, chloroquine therapy has been far less effective than corticoid therapy in the treatment of idiopathic nephrotic syndrome.

National Heart Institute,
National Institutes of Health,
Bethesda 14, Maryland, U.S.A. HOWARD C. GOODMAN
JAMES H. BAXTER.

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"LIVER FUNCTION"

SIR,—The references in your leader of Aug. 23 to fractional determination of bilirubin pigments may be regarded as misleading, even when allowance is made for brevity.

Firstly, it is not clear whether by fractional determinations is meant chromatographic separation by one of the methods of Lathe and his coworkers, or the more familiar one-minute and total bilirubin levels which have been advocated by Watson and others.[1 2] In either case the implication that the method has yet to be used as a test of liver function is misleading. Results obtained with the chromatographic method in the differential diagnosis of regurgitation jaundice [3 4] have been disappointing since there is considerable overlap in the patterns found in hepatitis, in extrahepatic biliary obstruction, and in jaundice due to malignant metastases. Neither of the reported studies can be regarded as exhaustive, yet it is my opinion that in the differential diagnosis of jaundice chromatographic separation of the serum bile pigments gives no useful information that cannot be obtained more simply by a total bilirubin estimation with specific attention to the type of van den Bergh reaction, and the performance of a simple but sensitive test for bilirubin pigments in urine. Your more optimistic attitude may be justified if a method can be found to separate and estimate the bilirubin pigments without preliminary precipitation of the plasma-proteins.

It is wrong to suggest that fractional determination of bilirubin pigments is a necessary investigation in the differentiation of the two rare conditions known as the Dubin-Johnson syndrome [5 6] and Gilbert's disease. In Gilbert's disease the van den Bergh reaction is negative and bilirubinuria absent: in the Dubin-Johnson syndrome the reaction is positive and bilirubinuria is usual. More complex methods give results in accord with these simpler observations but are no more certain. Where the total concentration of bilirubin pigments is less than 3 mg. per 100 ml., as it commonly is in these two conditions, chromatographic separation may be impossible or inaccurate.

Medical Research Council Group for Research on the General Effects of Radiation, Department of Radiotherapy, Western General Hospital, Edinburgh, 4. A. G. BAIKIE.

HAZARDS OF CHLOROTHIAZIDE THERAPY

SIR,—The warning of Professor Rosenheim and Dr. Ross (July 26) is timely. Apart from the cases they mention there is another group of patients who may respond well to the drug but in whom unexpected hazards may arise as a result of its use. I refer to those patients with hepatic cirrhosis with ascites and œdema who may have a most satisfactory diuresis on chlorothiazide with initial relief of symptoms. In these cases the danger appears to be that hypokalæmia may occur and precipitate the onset of hepatic failure and even hepatic coma, as occurred in a case I observed.

A man of 62, who was known to have had cirrhosis of the liver for several years, was admitted with ascites and gross œdema. There was considerable diuresis on chlorothiazide therapy which was measured by a fall in weight from 238 lb. to 219 lb. in ten days. After this the patient felt greatly improved, but fourteen days after admission he became restless, tremulous, and confused and obviously on the verge of hepatic coma into which he passed in twelve hours. At the time these symptoms began the serum-potassium was 4·5 mEq. per litre, but even after the chlorothiazide had been withdrawn the level continued to fall, the lowest figure being 2·9 mEq. Intravenous therapy with 20% glucose solution and added potassium chloride resulted in his recovering consciousness although he unfortunately relapsed two weeks later and died.

The only obvious precipitating cause of the hepatic coma was the lowered serum-potassium level, so that in cases such as this it seems as important to combine potassium chloride therapy as in cases of cardiac œdema treated with this diuretic.

London, W.1. JOHN LISTER.

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INDUSTRIAL MEDICINE AND GENERAL PRACTICE

SIR,—In a leading article in *The Times* of Aug. 4, the contention of Dr. Stephen Taylor (now Lord Taylor) that "a large part of Industrial Medicine is neither more nor less than General Practice . . ." is quoted, with approval, and on this basis a case is built up for the development of industrial medicine along these lines. Of course, Lord Taylor is entitled to his opinion, but as is well known this was not the view expressed in the report of the Committee of Enquiry on Industrial Health Services (the Dale Committee). The true function of industrial medicine, of course, is to advise management, and to suggest that it is just a form of general practice can only do harm by misleading both physicians and industrialists. The fact is that there is really no place at all within the factory for general practice, which should be undertaken by the proper person, who is the family physician; any other arrangement will only undermine his authority to the patient's disadvantage. In any case, the industrial physician should have something better to do than to seek to duplicate facilities already available through the National Health Service. This is not to say that the family physician has no part to play in an industrial medical service, but it is not that of general practice.

Medical Department, The Butterley Co. Ltd., Ripley, Derby. G. F. KEATINGE.

VAGOTOMY IN HYPERTROPHIC PULMONARY OSTEOARTHROPATHY ASSOCIATED WITH BRONCHIAL CARCINOMA

SIR,—Mr. Huckstep and Dr. Bodkin, in their interesting article of Aug. 16, report regression of bilateral gynæcomastia after vagotomy in a case of inoperable bronchial carcinoma. I would like to record a similar experience.

A man, aged 70, was admitted in April, 1958, to Baguley Hospital with carcinoma in the left upper lobe; clubbing of fingers and toes, osteoarthropathy with mild symptoms, and bilateral gynæcomastia which had been present for five months. Both breasts were enlarged, firm, pyriform, and slightly tender.

A left thoracotomy was carried out by Mr. John Dark on May 7. The tumour was found to be extensively invading the chest wall; as a result of this and other considerations it was not possible to remove the tumour. The left vagal trunk, below the recurrent laryngeal branch, and the pulmonary branches were divided. Biopsy of the left breast was performed. The report (Dr. T. A. White) is as follows:

"The fibro-fatty tissue contains an abnormal number of breast ductules surrounded by loose periductal stroma which is infiltrated by chronic inflammatory cells. Some of the ducts are dilated; many show marked epitheliosis, some papillary outgrowths are present in the lumina, and some ducts are almost filled by hyperplastic epithelium. No mitoses are seen in the sections; there is no evidence of extraductal invasion or of carcinoma. The appearances are consistent with a diagnosis of gynæcomastia."

Following operation, the gynæcomastia gradually regressed. The patient was seen again on Aug. 22. Although his condition

is deteriorating, there is now no gynæcomastia and there are no symptoms of osteorathropathy. Although forward curvature of the nails is still present, the pulp volume appears to have decreased, as is shown by longitudinal wrinkles on the finger-pads.

Baguley Hospital, Manchester, 23. LESLIE DOYLE.

PLEURAL BIOPSY

SIR,—In your annotation of Aug. 23 you mention two American reports on the value of this procedure, based on series of 23 and 31 cases. Perhaps you will allow me a little space to give a brief outline of the findings of Dr. A. C. Pollard, Dr. M. J. Purves, and myself. Our results will be fully reported in two papers submitted for publication several months ago.

We have carried out needle biopsy of the pleura in 200 patients, 152 of whom had a pleural effusion of unknown origin. In these 152 cases, biopsy gave the diagnosis in 101 cases: 70 were tuberculous and 12 malignant, and 10 were due to acute pyogenic infection only. The series contained at most 85 tuberculous pleural effusions: 70 were diagnosed on the histological appearances of the biopsy specimen and 3 on the results of pleural-fluid culture, while in 12 cases the diagnosis remained a presumptive one only. Of the 70 cases with a positive tuberculous biopsy, confirmation was obtained by a positive pleural-fluid culture in 25.

It is clear that pleural biopsy is by far the most reliable diagnostic measure in suspected tuberculous effusions, and is very worth while in all other pleural effusions whose cause is not obvious. We estimate that blind needle biopsy can be expected to give the diagnosis in 80% of primary tuberculous pleural effusions, and in more than 60% of malignant effusions. Where a strong clinical suspicion of primary tuberculous effusion exists, and needle biopsy is negative, full surgical biopsy of the pleura should be done; a patient should not be condemned to a long course of chemotherapy on presumptive evidence alone, for there can be no doubt that in a number of cases such evidence misleads.

Churchill Hospital, Oxford. PAUL MESTITZ.

PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—I have been following with considerable interest the correspondence on this subject. It appears that your correspondents are making an initial assumption open to serious doubt. This assumption is that the pain of "lumbago" is due to some change in the actual disc itself. Mr. Charnley (July 5) put the problem in a nutshell: "One of the most surprising things about acute lumbago is that the amount of pain does not seem to be proportional to the amount of organic change visible in the disc"; and, later in his letter, "we rarely found convincing protrusions in these cases but what is cogent to the present argument is that the material removed appeared more often to be normal than fibrous and stringy".

The argument about hyperhydration or desiccation as the cause of disc protrusion seems largely to be influenced by the theory that it is a rise in intra-disc tension that causes acute lumbago. I submit that there is far too little foundation for this assumption. Kellgren [1] and Whitty and Willison [2] have shown that pain of a variety of types can be produced reflexly from the muscles (or, as Sinclair et al.[3] prefer, the nerves within the muscles) of the back. Is it not time that we investigate more carefully the part played by other parts of the invertebral joint in the production of symptoms such as acute lumbago?

Gloucester. J. F. BOURDILLON.

1. Kellgren, J. H. *Lancet*, 1949, i, 943.
2. Whitty, C. W. M., Willison, R. G. *ibid.* Aug. 2, 1958, p. 226.
3. Sinclair, D. C., Feindel, W. H., Weddell, G., Falconer, M. A. *J. Bone Jt Surg.* 1948, **30B**, 515.

HOOKWORM AND ANÆMIA

SIR,—We have read with great interest the recent correspondence on this subject.

We do not suppose that there is any dispute that a sufficiently large hookworm load will cause anæmia.

Dr. Tasker's figures [1] suggest that a relatively moderate load of 800 worms may cause a daily loss of 80 ml. of blood. We have frequently counted 1000–3000 worms in the stools after giving a vermifuge. Hookworm infection is so widespread in Africa that, although probably only a small proportion of those infected carry a sufficient load of worms to cause clinical anæmia, this small proportion is in absolute numbers so large as to constitute, in many places, a serious medical problem.

We have recently carried out some observations which show that heavy, but not light, hookworm loads cause a demonstrable fall in the absorption of nitrogen from the intestine. Ventkatachalam and Patwardhan [2] have shown that ascaris can behave similarly, and Stewart [3] showed that *Hæmonchus contortus* diminished nitrogen absorption in the sheep. Various authors have claimed that ascaris secretes an antiproteolytic substance into the intestine, and Stewart has claimed that *H. contortus* does this in the sheep. So far as we are aware, the question of the production of an antiproteolytic substance by hookworms has not yet been investigated.

Apart from any effect of parasites, there is evidence that a diet low in protein by itself decreases nitrogen absorption.[4–6]

May not the sequence of events be somewhat as follows? In a population exposed to hookworm infection, those on a diet poor in protein secrete a diminished amount of proteolytic enzymes in the intestine. Hookworms, on reaching the gut, thus find it relatively easy to establish themselves. They produce their antiproteolytic substance, still further damaging the host's power of absorbing nitrogen, and therefore his power to secrete digestive enzymes, so setting up a vicious circle. Presumably the diminution of proteolytic enzymes will encourage the lodgment of fresh worms. Conceivably protein depletion may also hamper the host's resistance to invasion by the infective larvæ. Removal of the worms with the administration of iron will cure the anæmia—until reinfection occurs.

Such a hypothesis would help to explain the observation that in some communities the percentage of persons harbouring hookworms is very high, but heavy loads and gross anæmia are rarely seen, and that those with heavy worm loads and gross anæmia so often give a history of having lived on a diet greatly deficient in protein.

East African Medical Survey and Research Institute, Mwanza, Tanganyika. E. G. HOLMES
S. J. DARKE.

SIR,—We have estimated the blood and iron losses in the stools of anæmic and non-anæmic patients with heavy, light, and no hookworm infection. This has been done over periods of 40 to 50 days before giving a vermifuge and for 10 to 30 days afterwards.

The blood and iron content of the stools were estimated using ^{59}Fe ($FeCl_3$) and ^{51}Cr (Na_2CrO_4) by the recognised techniques modified to meet our special requirements. 10–15μc

1. Tasker, P. W. G. *Lancet*, 1958, i, 1226.
2. Ventkatachalam, P. S., Patwardhan, V. N. *Trans. R. Soc. trop. Med. Hyg.* 1953, **47**, 169.
3. Stewart, J. Report of Director of Institute of Animal Pathology, Cambridge, 1932–33; p. 77.
4. Thompson, M. D., Trowell, H. C. *Lancet*, 1952, i, 1031.
5. Platt, B. S. Report of Second Inter-African (C.C.T.A.) Conference on Nutrition, Gambia, 1952; p. 153. H.M. Stationery Office, 1954.
6. Pellet, P. L. *Proc. Nutr. Soc.* 1957, **16**, x.

of ^{59}Fe and 100 μc of ^{51}Cr were given intravenously either as ferrated plasma or chromated cells and thereafter the whole stool collected daily. The radioactivity was measured on each stool separately using a ring of six 10-inch halogen-quenched Geiger-Muller tubes. The stools were then dried and powdered and re-read in the counter, as well as in a plastic wrap-round pot in a scintillation counter, using a thallium-activated sodium-iodide crystal. Plasma-volumes, red-cell mass, and iron clearances and utilisation were determined and the expected pattern for hypochromic anæmias found.

The following data refer to an anæmic adult male African patient with many hookworm eggs in the stool who entered hospital on May 23, 1958. Hæmoglobin (Hb) 3·7 g. per 100 ml., mean corpuscular Hb concentration 25%, packed-cell volume 14%; a very active erythronormoblastic sternal marrow. Free HCl in gastric juice. Given 1·0 g. (gr. 15) of ferrous sulphate daily from May 29 to July 30. Hookworms still present but Hb rose to 14·6 g. per 100 ml. on July 8. Blood and iron losses during the 39 days before worming totalled 470 ml. and 171 mg. respectively (mean daily loss 12 ml. and 4·4 mg.).

Daily losses of blood were extremely variable (1·6 ml.–25·0 ml.) emphasising the desirability of daily measurements. As was to be expected, the iron losses increased as the Hb level rose, so that a similar blood loss will result in a greater iron loss in less anæmic patients.

On July 8 the patient was given a vermifuge of tetrachlorethylene followed 3 hours later by a magnesium-sulphate purge. 1100 *Necator americana*, 2 *Tænia saginata*, and a few ascaris were recovered from the stools passed during the next 48 hours. A second vermifuge was given on July 25, but no hookworms or other parasites were recovered.

The blood and iron losses were similarly estimated for 13 days after the vermifuge, and gave a total blood-loss of 24 ml. and an iron loss of 12 mg. with mean daily values of 1·8 ml. and 0·9 mg.

Since there are considerable intestinal mucosal losses (30–80 g. daily) some part of the fæcal iron may have come from this source; in patients with heavy worm loads mucosal desquamation rates may be higher than in non-infected patients.

The amount of radioactivity found in the hookworms was equivalent to approximately 0·002 ml. blood per worm (=0·005 mg. Fe). We do not regard this figure as in any way significant, since it is not the amount of blood that the worms consume that is important but their migratory browsing habits which may leave bleeding points in the mucosa and the possibility that they may " pump " blood through them in the act of sucking.

Taking into consideration the variations in the hæmoglobin level during the whole period of observation before de-worming, 9·0 mg. of Fe were lost in the first 13 stools passed after the dose of ^{59}Fe with a mean hæmoglobin during this period of 4 g. per 100 ml.; in the following 13 stools taken during the period when the average hæmoglobin was 7 g. per 100 ml. 18 mg. of iron were lost; in the next 13 stools taken during the period when the hæmoglobin was 12 g. per 100 ml., 74 mg. of Fe were lost, and in the final 11 stools collected when the hæmoglobin was 15 g. per 100 ml., 70 mg. were lost. Thus during the 39 days prior to the removal of the 1100 hookworms, 171 mg. of iron were lost—a daily average of 4·4 mg. In spite of heavy hookworm loads only on two occasions did the daily loss of blood exceed 20 ml. (25 ml. and 23 ml.) and this when the hæmoglobin level was 4·0 g. per 100 ml., thus giving an iron loss on these two days of only 2·5 and 2·0 mg.

In the 13 days following the removal of the worms the patient lost 24 ml. of blood and 12 mg. of Fe, taken at a 15 g. per 100 ml. hæmoglobin. He was discharged from hospital on July 26 with a hæmoglobin of 15·0 g. per 100 ml.

From the above facts it seems that:

(1) Normal hæmoglobin levels can be attained in very severe iron-deficient anæmia by giving oral iron therapy alone while leaving the worms in situ even in cases such as the above that have heavy hookworm loads.

(2) There are wide daily variations in the amount of blood and iron lost.

(3) Heavy hookworm loads do not always produce significant blood and iron losses, and that there is not always a correlation between worm loads and blood-loss. This blood-loss can be diminished by either iron treatment or transfusions, while leaving the worms in situ, indicating that worms are not the only factor involved.[1,2]

(4) Iron losses, although diminished, may continue after the removal of the worms, perhaps owing to the temporary persistence of bleeding points in the gut.

(5) Similar blood-losses give rise to higher iron losses as the hæmoglobin of the patient rises, a point not always appreciated.

(6) Some of the iron liberated from the blood in the gut may be reabsorbed, although hæmoglobin is not a good course of iron.

(7) Intestinal cellular desquamation may be high in parasite-infected patients and may account for some of the iron lost.

It should not be concluded from this example that all patients having hookworms are anæmic or that all patients with iron-deficient anæmias in the tropics have hookworm.

Full details of this work will be published elsewhere with the findings in anæmia without hookworms and in non-anæmic patients with hookworms.

Wellcome Trust Research Laboratories and Government Electrical Engineering Department, Nairobi, Kenya.

HENRY FOY
ATHENA KONDI
W. H. AUSTIN.

NEUROTROPIC VIRUS IN AFRICAN MONKEYS

SIR,—In view of the increasing use of African monkeys for tissue-culture purposes, we wish to record that a virus resembling the B virus of Sabin and Wright [3] has been isolated twice in these laboratories from central-nervous-system tissues of the African vervet monkey *Cercopithecus æthiops pygerythrus*.

This virus produces nuclear inclusions and small syncytia in cultures of monkey-kidney epithelium. The intradermal and subcutaneous inoculation of rabbits is followed by marked necrosis of the skin and, in some instances, by paralysis and death; and the virus has been recovered from the brains and spinal cords of rabbits showing paralysis. Neutralisation tests with anti-B virus sera indicate that there is a serological relationship between B virus and the agent we have recovered, which we have designated SA8 in the series already described by us.[4]

Laboratories of the Poliomyelitis Research Foundation, South African Institute for Medical Research, Johannesburg.

H. MALHERBE
R. HARWIN.

UNSATURATED FATS AND IMPORT RESTRICTIONS

SIR,—Dr. Bourdillon (Aug. 23) is incorrect in stating that patients in Britain are unable to purchase corn oil. Maize oil (corn oil) *B.P.C.* is freely available for purchase by patients at retail chemists in the United Kingdom. A simple, palatable emulsion containing approximately 50% of maize oil *B.P.C.* can also be obtained by those who dislike the taste of pure maize oil.

Both preparations are being prescribed. A number of long-term clinical studies are also being carried out at different centres in view of the observation that the ingestion of certain vegetable oils will result in the lowering of a raised serum-cholesterol. Published work suggests that maize or corn oil, given in adequate quantity, is probably the most active of these vegetable oils in its cholesterol-lowering property.

1. Roche, M., et al. *J. clin. Invest.* 1957, **36**, 1183.
2. Roche, M., et al. *Nature, Lond.* 1957, **180**, 1078.
3. Sabin, A. B., Wright, A. M. *J. exp. Med.* 1934, **59**, 115.
4. Malherbe, H., Harwin, R. *Brit. J. exp. Path.* 1957, **38**, 539.

It is to be hoped that as a result of such careful clinical investigations the practical value of maize oil in the treatment and prophylaxis of atherosclerosis will be properly assessed.

Medical Department, Boots Pure Drug Co. Ltd., Nottingham. E. V. B. MORTON.

HOW TO BE HAPPY THOUGH RESIDENT

SIR,—I wish I had been able to read Mr. Bryan Jennett's article, in your last issue, five years ago when I first qualified. I am sure it will save all new housemen who read it from finding out many things the hard way when they start in hospital.

Putting yourself in the other person's position, writing down things clearly in case-notes, and dealing with the proper people are but three pieces of advice which in retrospect are invaluable.

Liverpool. C. R. PORTEOUS.

Public Health

Influenza this Winter

MEETING in Stockholm recently with Dr. C. H. Andrewes as chairman, the World Health Organisation's expert committee on respiratory virus diseases said that the A/Asia/57 virus is likely to be the predominant type in influenza outbreaks during the next few years. People infected during the pandemic of 1957 are likely to have at least a basic immunity.

Large quantities of vaccine, providing 60–70% protection, are now available in several countries. From a clinical standpoint, its use is especially important for expectant mothers and people suffering from cardiovascular or lung disease, or metabolic disorders. To offer maximum protection, it should be given at least a fortnight before influenza is expected to become epidemic. There can be no question of stopping an epidemic by vaccination: what is aimed at is limitation of its effects by preventing high death-rates and excessive absenteeism, such as might disorganise public services.

Vice-chairman of the committee is Prof. V. M. Zhdanov, of Moscow, and, among other advances in vaccine research, work in the U.S.S.R. with attenuated live virus vaccines was reviewed. Unlike the formalin-inactivated influenza virus, the live vaccine is not administered by inoculation but sprayed into the nose and throat. Because of its high virulence, it is not recommended for children under 7 years old.

Mention was made of a method—promising but unproven—by which stocks of vaccine may be made to go further by mixing with an "adjuvant". The possibility of an animal reservoir of human influenza was also discussed. Several studies of this, initiated by W.H.O., are in progress.

Carbon Dioxide in Harvested Grain

The Ministry of Agriculture, Fisheries, and Food has pointed out that grain harvested wet may give off carbon dioxide. This can happen in any place where grain is stored, and the gas, being heavier than air, will collect in the pits or ducts of a grain-handling plant. When carbon dioxide is detected by the extinction of a lighted match or candle, the place must be thoroughly ventilated. Anyone working in these places who feels faint or dizzy should get out at once.

Preservation of Citrus Fruits

The Minister of Agriculture, Fisheries, and Food and the Minister of Health, acting jointly, have made the Public Health (Preservatives, &c., in Food) (Amendment) Regulations, 1958, which permit the importation and sale of citrus fruit containing diphenyl or ortho-phenylphenol or admixtures of the two substances within prescribed limits.

Obituary

CHARLES CADY UNGLEY

M.D. Durh., F.R.C.P.

Dr. Ungley, who died at the age of 55 in the Royal Victoria Infirmary, Newcastle upon Tyne, on Aug. 21, was a general physician, skilled especially in hæmatology and neurology, who in the midst of general hospital duties, teaching, and (for many years) private practice maintained a passionate interest and immense industry in research.

He qualified in Newcastle in 1925, and, after a trip to the Far East as a ship's surgeon, he held resident appointments at the Royal Victoria Infirmary, taking his M.D. in 1927 and his M.R.C.P. in 1928. His research ability was soon apparent, and in 1930, with a Rockefeller studentship, he visited America, working at Harvard University and at the Massachusetts General Hospital. He was appointed to the staff of the Royal Victoria Infirmary in 1933 and in 1935 was awarded a Leverhulme scholarship of the Royal College of Physicians to study pernicious anæmia. In 1937 he was elected F.R.C.P., and in the following year he gave the Goulstonian lectures, on deficiencies of nutrition and their relation to disease.

His chief interest was in pernicious anæmia and he developed fundamental techniques for the clinical assay of liver fractions. As a by-product of this work he provided the Royal Victoria Infirmary with a first-class hæmatology service. During the late war he served with the Navy, and his work on survival at sea was, and remains, of the highest importance. It was based on immense labour in the collection of data, and included his special study of immersion foot. But after the war he returned to pernicious anæmia and was at hand with a fully developed organisation for the first clinical trials of vitamin B_{12}. His work on the comparison of vitamin B_{12} and liver extract in the treatment of subacute degeneration was an outstanding example of the careful elicitation of neurological signs and their expression in quantitative terms. At the end of his life he was trying to extend this work using serial psychometric tests to study vitamin-B_{12} deficiency in the brain. Of his continuous interest in this research F. J. N. writes:

"Charles Ungley was at once fascinated by the report by Minot and Murphy of the efficacy of liver diet in the treatment of pernicious anæmia and was one of the first to demonstrate the remarkable improvement which could often be obtained by early treatment of subacute combined degeneration of the cord with liver. One of his earliest papers, published in the *Newcastle Medical Journal* in 1929, was on this subject. He continued with this work after the war and the results of his most meticulous studies were published in *Brain* in 1949. The great developments of hæmatology opened up by the discovery of the liver treatment found him in the forefront of clinical and experimental research. Under the stimulus of Castle's hypothesis he strove to determine the nature of the extrinsic and intrinsic factors, and, most notably, collaborated with Lester Smith in testing the potency of purified liver extracts and ultimately of vitamin B_{12}."

Ungley was deeply conscious of his responsibilities to his students. His firms were always happy ones. He enjoyed teaching and was good at it, and those who came

to his ward, especially on a Saturday morning, were well rewarded. Himself a specialist of specialists, he was determined that his ward clerks should see medicine in a wider setting, and, long before it became official policy to do so, he used to arrange for them to visit a number of general practitioners during their appointment. Of this scheme A. S. relates:

"Ungley approached four general practitioners (of whom I was one), with urban, semi-urban, rural, and small-town practices, and persuaded each to take a student for one day weekly and show him something of general practice. This scheme differed from most others which have been introduced since, in that the student saw different types of practice and different doctors, and saw them at the beginning of his hospital career. This made him realise that patients are people with homes and families, not merely vehicles of disease, and coloured his later dealings with patients in hospital."

The affection, as well as respect, which Ungley inspired is shown by R. E. I.'s words about his old chief:

"Charlie's figure was slight and athletic, his manner diffident, and he always looked a little windswept (he loved to drive an open car). Any conversation was punctuated by the frequent lifting of his eyebrow to a fascinating height. His later years were dogged by illness, but he never allowed this to diminish his appetite for life. A few years ago he took up gliding, and his pleasure was infectious when he passed the tests that entitled him to fly solo. When ill health put an end to flying he took up art, and in the last year of his life achieved some notable oils. Despite his world-wide reputation he remained the most modest, lovable, and approachable of men, and he always retained something of the simplicity of childhood. He was sometimes shy with adults but he was always at home with children and they loved him. No-one who saw him dancing with a little girl who came downstairs in her nightgown in the middle of a party, or who watched him cooking sausages at a family picnic, could doubt that, stricken though he was in health, he would never lose the secret of youth. To work with him was to receive a priceless education in clinical investigation; it was also to have contact with a human spirit of the rarest quality."

Dr. Ungley leaves a widow, a son, and two daughters.

HUGH ARTHUR SANDIFORD

M.C., M.B. Manc., D.P.H.

As the first director of Army psychiatry and again as the first director of the Commonwealth and the International Advisory Bureaus of the British Medical Association, Brigadier Sandiford proved his worth as a pioneer medical administrator.

He was born at Manchester in 1892 and educated at the grammar school and university of that city, qualifying in 1914. Almost at once he joined the R.A.M.C., and in 1917 he was awarded the M.C. for gallantry while looking after casualties under heavy artillery fire. After the war he decided to remain with the R.A.M.C., and in the next years he gained valuable experience both of clinical medicine and of administration. In 1925 he took the D.P.H. and in 1933 he was appointed instructor at the Army School of Hygiene. Later he became assistant director of hygiene at the War Office and deputy director of hygiene in Eastern Command.

At the beginning of the late war his wide experience of physical assessment persuaded him of the importance of devising suitable methods of selection, and his interest in this task led in due course to his appointment as director of Army psychiatry at the War Office. His success in what was not an easy assignment was appreciated by his psychiatric colleagues, one of whom, T. F. R., writes:

"It is no secret that the rise of psychiatry during the early years of the war was viewed with disquiet by many senior members of the Army Medical Services. When it became necessary nevertheless to provide adequate administrative arrangements for these developments, it was a relief to many to know that a Regular as wise and as moderate as Sandiford had been appointed director of Army psychiatry. To our surprise we psychiatrists quickly learned that we had acquired a good friend whose understanding and confidence in the potential value of the contribution we could make to preventive medicine was greater than our own. He may have exerted a steadying influence upon us, but—what was far more important—he inspired us to work in new directions. His own World War I experience led him to take a special interest in the problems of repatriated prisoners of war and, as a result, psychological studies were made which resulted in the setting up of civil resettlement units towards the end of the war. The experience thus gained has led to many other experiments in rehabilitation of a similar kind and to the setting up of other therapeutic communities, but the first insight which led to these experiments in social psychiatry we owe to Sandy. He was a quiet man whose sincerity and integrity showed itself in all his actions, and he very easily won the trust and affection of all who worked with him."

During his years in the Army he had met and worked with medical officers from many parts of the world, and especially of course from the British Commonwealth. When, in 1947, shortly after he retired from the Army, the B.M.A. decided to set up their advisory bureaus to help medical visitors from abroad Sandiford was chosen, from over a hundred applicants, as director of the new venture. His talents for kindliness and organisation complemented each other, and he offered those who came to the bureaus a friendly welcome backed by useful information and practical advice. Of this second stage of his career a colleague writes:

"Sandiford was well suited for his work at the B.M.A. He was shrewd and often blunt; but he was above all a kindly man, interested in human affairs. His work bore the mark of the skilled administrator; but, unlike many administrators, he was capable of the liveliest initiative when need arose. The need did arise when Hungarian doctors began to arrive in this country as refugees in the autumn of 1956. Of the two score or so who reached here, nearly all soon found their way to Sandiford's office. No matter what their needs—a passage to South America, thirty shillings for a train fare, accommodation in Scarborough, a new suit, news of relatives in Budapest, a job in Bristol—Sandiford did his best, and, because (despite his genial air) he did not shrink from ruthless unorthodoxy, he usually succeeded. The ripples of the Hungarian revolution have died away; but it is certain that the doctors who then came to England will not forget Sandiford—equable, courteous, benign, and wise, always ready to listen and to act."

Brigadier Sandiford retired from his work with the B.M.A. last year and he died on Aug. 13 at his house in Windsor. He leaves a widow, two daughters, and a son, Dr. R. H. Sandiford.

Dr. J. BROCK BISHOP

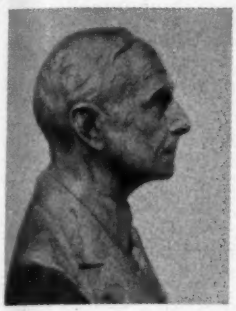
P. G. McG. writes:

"Brock Bishop had a tremendous zest for the full life. His interests were wide, and to each one of them—social, professional, and purely recreational—he gave a full measure of his abundant energy. I saw this mainly in his medical work, where his conscientious attention to every facet of the life of his patients not only paid handsome clinical dividends, but earned him the respect and deep affection of patients and colleagues. His devotion to duty did not result in a dreary rigidity, but was clothed in a vivid, flexible human approach; the patients' own attitude and susceptibilities would extract from Brock the formal courtesy of which he was a master, or through the whole gamut to a friendly raciness of language which on occasion enlivened his reports as well. The memorial which he would appreciate most is the affectionate smile which comes to every face in Broadmoor at mention of his name."

CHEVALIER JACKSON

M.D. Jefferson, D.Sc. Penn., LL.D. Temple

Chevalier Jackson was born in Pittsburgh in the last year of the American Civil War. As a frail sensitive child he was shocked by the brutal sports and cruelty of the farming and coalmining community in which he grew up, and at school he was exposed to merciless bullying. The misery of these years was mitigated by the happiness of his home where he was encouraged to read, to draw, and above all to make things.



He began to use wood and sharp tools at the age of four and thereafter, he wrote, "I was never without a workshop; later it was called a laboratory, but it was always a place for constructive work." Carpentry was his first manual skill. In the next difficult years he acquired others; and his thrifty genius wasted none. At the family hotel he was put in charge of the uncertain gas-generating plant and water system. To fit himself for this task he served a summer vacation as a plumber's apprentice. His experience with tubes and valves led later to his discovery that in the heart and lungs there are mechanisms parallel to the stop valves, by-pass valves, and check valves of pipes, pumps, and plumbing. "My whole life's work with the air and food passages seems curiously parallel in its fundamentals to those boyhood days as a plumber's cub." To earn money to pay for his first year at college he worked as a china and glass decorator, painting apple blossom and butterflies on lamp shades and stands. Later this talent allowed him to reproduce what he saw for medical illustrations in colour.

His medical training was only accomplished with difficulty. After a year with a "preceptor", Dr. Gilmore Foster, he entered Jefferson College, Philadelphia, in 1884. When his fees had been paid, he was left with 63 cents a day for all his other expenses. In the long vacation he sold medical books on commission, and sailed as ship's cook to the cod-fishing in Newfoundland. The M.D. course in those days was two years, and he graduated in 1886 still six months short of the legal age of twenty-one.

The new graduate had already chosen his specialty. A dispensary for diseases of the ear, nose, and throat had lately been set up in Philadelphia, and as a student he had attended it regularly. His teacher, Dr. J. Solis Cohen, had lent him a complete set of the writings of Morell Mackenzie; and he decided without delay to visit Mackenzie's clinic in London. He accumulated a little money and sailed steerage for Europe and London. He stayed as long as his funds held out, and on his return to Philadelphia boldly set up in consultant practice.

To begin with, much of his practice was among the children of the poor. The value of tonsillectomy was becoming more widely recognised, and Chevalier Jackson was so convinced of its merit that he offered to examine and operate on the children in the local schools. In those days, too, stricture of the larynx was often the tragic sequel to diphtheria, and he won a reputation for his skill in treating these children by tracheotomy and by intubation. In nearly every American kitchen lye was used as a cleaning material. It looked like sugar and too often it stood unlabelled, tempting, and unguarded. If a child put it in his mouth, the œsophagus was burnt and the contracting scars gradually closed the passage till the child died of starvation. The misery of these small patients led Chevalier Jackson to embark on his long campaign (which only succeeded in 1927) to make it compulsory that preparations containing this dangerous substance should carry a poison label and a warning to keep them out of the reach of children.

In treating these small patients he used an instrument which he had adapted from a device he had first seen in Morell Mackenzie's clinic. In his hands the instrument was improved; a light carrier was added, and it became the œsophagoscope. As well as for lye strictures he used it for the removal of foreign bodies. For his diphtheria patients he was already using a laryngoscope, and his skill and success with these instruments led him to the study of bronchoscopy. His belief in the value of these new techniques forced him into the role of teacher and soon he was giving bronchoscopic courses in Pittsburgh, Philadelphia, and Paris.

In 1911 his work was restricted, though not interrupted, by his first attack of tuberculosis. He was ordered to supplement his austere diet and to spend 12 out of every 24 hours in bed. Though much of his bed rest was spent in annotating his case-records and making sketches of laryngeal and endoscopic views of pathological tissue, his infection was halted and in six months he was back at work. But two years later he had a recurrence, and renewed bed rest was ordered. With some misgivings, for the sake of his health he gave up the most remunerative part of his practice—tonsil and adenoid operations—and henceforth limited his specialty to laryngoscopy, bronchoscopy, œsophagoscopy, and gastroscopy. He also used his enforced rest to write his book on *Peroral Endoscopy and Laryngeal Surgery* which was published in 1915.

As early as 1900 he had been elected to the chair of laryngology in the Western Pennsylvania Medical College, later the University of Pittsburgh, and with the years his reputation grew steadily. In 1915 the New York Post-graduate Medical School appointed him professor of bronchoscopy and entrusted him with the organisation of a new department of bronchoscopy, but he had only held this chair a short time when his third attack of tuberculosis forced him to resign. Despite his uncertain health, in 1916 he made the decision to "pull up stakes" and move from Pittsburgh to Philadelphia, where he had been offered the chair of laryngology at Jefferson College. Academic posts then offered prestige and opportunity but no salary, and the move meant giving up a private practice which was just beginning to be lucrative to start again from the beginning. But his welcome from his colleagues in Philadelphia heartened him, and three years later the University of Pennsylvania created for him a chair of bronchoscopy and œsophagoscopy, and in 1924 Jefferson College followed their example. To this formidable array of chairs, almost all specially endowed for him, he later added chairs at Temple University and at the Women's Medical College of Pennsylvania (of which he was also president).

He accepted his responsibility as one of the founders of a new specialty and travelled all over the world to give lectures, attend conferences, and share in discussions.

Many of his colleagues in this country will still recall his address to the British Medical Association at Bath in 1925. One of them later wrote [1]: "The slight puckish figure, clothes loosely fitting and collar two sizes too large . . . with a rubber mannikin and gleaming instruments, drawing chalk diagrams with both hands, showing more and more lantern slides and

1. Scott Stevenson, R. In a Harley Street Mirror; p. 140. London, 1951.

short cinema films, and talking and talking with enthusiasm, straight on for two hours." On many of his journeys he received professional, academic, and national honours. His appointment as officer of the Legion of Honour of France was particularly appropriate, for he was linked to that country by ties of kinship.

In his private life, too, Chevalier Jackson was always aware of his specialty. His simple and austere life may not have been uncongenial, but abstinence from tobacco and alcohol, his abstemious, vegetarian meals, his habit of wearing gloves, all safeguarded the dexterity of his sensitive fingers and the steadiness of his eyes and nerves.

Soon after he came to Philadelphia he and his wife settled in an old grist and saw mill about 35 miles from the city. With characteristic ingenuity the grist mill was repaired and induced once more to earn its keep and to provide the house with electricity. In this family retreat Chevalier Jackson was able politely to evade unwelcome social engagements (and nearly all social engagements were unwelcome) and to spend his time in his workshop, writing in a boat on the mill stream, and reading or painting at his study window where he shared the sill with rabbits, quails, and birds.

He died on Aug. 16 in the hospital of Temple University, Philadelphia, where his son, Dr. Chevalier L. Jackson, is now professor of laryngology and broncho-œsophagology.

One of his British colleagues, V. N., writes:

"The death of Chevalier Jackson marks the end of an epoch in advancement of the knowledge and treatment of diseases of the lungs and œsophagus. He added very greatly to methods which not only allowed of instrumentation within the air and food passages but also carried forward investigations into the physiology and pathology of these regions. His early days were ones of struggle and of financial difficulty; with tenacity of purpose he concentrated his energies on endoscopic methods in the trachea, bronchi, and œsophagus, though he had difficulty in convincing the medical profession of the importance of this approach.

"Of the many distinctions, both in America and in other parts of the world, which came to him, the most important included his election as honorary fellow of the Royal Society of Medicine of London, of the Scottish Society of Otology and Laryngology, and of the Royal College of Surgeons of Edinburgh; and as laureat of the Académie de Médecine of Paris. Perhaps one of his most illuminating honours was the conferring on him in 1952 of the Medallion of the American College of Chest Physicians, which emphasises the recognition by the medical profession of his extremely valuable contributions to the field of the chest physician and thoracic surgeon. His memory will be treasured by innumerable friends and students who for long have recognised the value of his pioneer work."

Our photograph is of a bust by Luigi Maraffi, presented to Chevalier Jackson by a group of his pupils and colleagues in 1937.

Appointments

BRADSHAW, D. B., M.B. Dubl., D.P.H.: M.O.H. and principal school M.O., Leeds.

CAMPBELL, R. J. C., M.B. Edin., D.M.R.: consultant radiologist, Stracathro Hospital, Brechin, Brechin Infirmary, Arbroath Infirmary, and other Angus area hospitals.

CECIL, J. T., M.B. Lond., D.P.H.: assistant M.O., Maidstone area, Kent.

GRIFFITH, EIRWEN, M.B. Lond.: assistant M.O., Medway towns area, Kent.

MANGAN, GEORGE, M.R.C.S., D.O.: ophthalmologist, Ongar, Epping, and Waltham Abbey refraction clinics.

MORRIS, P. A., L.A.H. Dubl., D.P.M.: senior assistant psychiatrist, Kingsway Hospital, Derby.

SMITH, D. ROBERTSON, M.D. Cantab.: consultant pathologist, Reading area pathology service.

SUMMERS, HARRY, M.B. Manc., M.SC. Brist.: assistant M.O., Mid-Cheshire area.

Notes and News

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved Name	*Other Names*
Ambazone	1:4-Benzoquinone amidinohydrazine thiosemicarbazone hydrate Iversal
Beclamide	*N*-Benzyl-*β*-chloropropionamide Nydrane
Benztropine	3-Diphenylmethoxytropane Cogentin is the methanesulphonate
Bisacodyl	Di-(*p*-acetoxyphenyl)-2-pyridylmethane Dulcolax
Chlorphenesin	3*p*-Chlorophenoxypropane-1:2-diol
Clenizole	1-*p*-Chlorobenzyl-2-pyrrolidinomethylbenzimidazole Allercur is the hydrochloride
Clemizole Penicillin	Benzylpenicillin combined with 1-*p*-chlorobenzyl-2-pyrrolidinomethyl-benzimidazole Megacillin; Neopenyl
Deanol	2-Dimethylaminoethanol Atrol is the bitartrate
Dimethisterone	6α:21-Dimethylethisterone Secrosteron
Ethoheptazine	Ethyl (±)-1-methyl-4-phenylaza*cyclo*heptane-4-carboxylate Zactane
Framycetin	An antibiotic derived from *Streptomyces decaris* Soframycin is the sulphate
Furazolidone	3-(5-Nitrofurfurylideneamino)oxazolidin-2-one Furoxone
Inproquone	2:5-Bisethyleneimino-3:6-dipropoxy-1:4-benzoquinone
Pempidine	1:2:2:6:6-Pentamethylpiperidine Perolysen is the hydrogen tartrate; Tenormal is the hydrogen tartrate
Phytomenadione	2-Methyl-3-phytyl-1:4-naphthaquinone Vitamin K_1 Konakion; Mephyton
Piprinhydrinate	Diphenylpyraline salt of 8-chlorotheophylline 4-Diphenylmethoxyl-1-methylpiperidine salt of 8-chlorotheophylline Kolton; Mepedyl
Sulphaethidole	5-*p*-Aminobenzenesulphonamido-2-ethyl-1:3:4-thiadiazole Sethadil
Sulphathiourea	*p*-Aminobenzenesulphonylthiourea Badional
Trimethidinium	(+)-3-(3-Dimethylaminopropyl)-1:8:8-trimethyl-3-a*zabicyclo* [3:2:1] octane di (methyl methosulphate) Camphidonium

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Proprietary Name	*Approved Name*
Allercur	Clemizole
Atrol	Deanol
Badional	Sulphathiourea
Camphidonium	Trimethidinium
Cogentin	Benztropine
Dulcolax	Bisacodyl
Furoxone	Furazolidone
Iversal	Ambazone
Kolton	Piprinhydrinate
Konakion	Phytomenadione
Megacillin	Clemizole Penicillin
Mepedyl	Piprinhydrinate
Mephyton	Phytomenadione
Neopenyl	Clemizole Penicillin
Nydrane	Beclamide
Perolysen	Pempidine
Secrosteron	Dimethisterone
Sethadil	Sulphaethidole
Soframycin	Framycetin
Tenormal	Pempidine
Vitamin K_1	Phytomenadione
Zactane	Ethoheptazine

INFANTILE DIARRHŒA AND VOMITING IN IRELAND

IN the Medical Research Council of Ireland's report for 1957,[1] Dr. Owen Conor Ward and Dr. Desmond Donovan describe a survey of the incidence and epidemiology of infection by the *Escherichia coli* strains which have been held responsible for communicable diarrhœa and vomiting in infants.

The investigation was started on the opening day of a new hospital—Our Lady's Hospital for Sick Children—at Crumlin. For nearly a year rectal swabs were taken on admission and then weekly from infants under the age of two—numbering 647 in all. These children were not drawn from one area: although most came from Dublin city, many were from country districts.

On admission, the rectal swabs of 69 patients were positive for the *Esch. coli* variants; of these 62 had diarrhœa or vomiting, or both. 329 patients had diarrhœa or vomiting but negative rectal swabs, and in 118 of these no satisfactory explanation of the symptoms was found. In general, these were not so ill as the children from whom escherichia strains were recovered: only 22 of the 329 were severely dehydrated (and 6 of these had been in contact with pathogenic *Esch. coli*) whereas 12 of the 69 swab-positive cases showed such dehydration.

All the infants were nursed in separate cubicles by trained staff, yet there was cross-infection with *Esch. coli* in at least 31 cases. Dr. Ward and Dr. Donovan conclude, therefore, that dissemination of the infection cannot be prevented by ordinary nursing techniques.

MEDICAL SERVICES OF PAPUA AND NEW GUINEA

IN our advertisement columns this week the Territory of Papua and New Guinea is advertising the post of assistant director of medical research. As local conditions of life and medical practice will be unfamiliar to many of our readers, the Director of Public Health has sent us some notes about them.

The combined territories, he points out, include half the mainland of New Guinea and all the islands to the north and north-east. Their area is 183,600 square miles and the population 1¾ million, of whom 18,000 are not Papuans. Communications by road are limited by mountains and fast-flowing rivers, but air services connect most districts.

The people live in villages and hamlets and depend on a subsistence economy, but primary and secondary industries are gradually raising the standard of living. The two most important diseases are malaria and tuberculosis. Others are filariasis, helminthiasis, amœbic and bacillary dysentery, leprosy, yaws, and venereal diseases, to which may be added such general medical problems as anæmia and pneumonia, with cirrhosis of the liver and kwashiorkor in certain areas.

The department of public health, with headquarters at the capital, Port Moresby, provides the curative and preventive services offered by local and central government health authorities in other countries. Its doctors also undertake some private practice, and there are other private practitioners in the main centres of Port Moresby, Lae, and Rabaul. The department is administered by a director, with assistant directors responsible for divisions of medical services, preventive medicine, medical training, infant child and maternal health, and administration. There is a European staff of 80 doctors, 146 medical assistants, 138 trained nurses, and 172 ancillary and clerical staff. The indigenous staff consists of 4500 Papuans and New Guineans: most of them are semi-skilled orderlies, with a gradually increasing educational level. The Christian missions also have a medical staff of 137, of whom 12 are doctors. There are 98 hospitals scattered over the entire territory, and 1200 aid posts or dispensaries in the villages.

Port Moresby General Hospital, the base hospital for the entire territory, is to be the centre for future medical research. It has 370 beds. The buildings are of a modern design including air-conditioned laboratories, theatres, and X-ray department. The medical staff consists of a medical superintendent, surgeon, anæsthetist, physician, ophthalmologist, pædiatrician, two radiologists, pathologist, chest physician, and 4 resident medical officers. The hospital is also a training centre. Nurses' training has begun and a medical school is to be opened in 1960 for assistant medical practitioners, along the same lines as the Central Medical School at Suva, Fiji.

The aim of the department is to improve the standard of public health in the villages and hamlets, and the emphasis is accordingly being shifted to preventive as opposed to curative medicine. But preventive medicine needs basic research into the problems to be controlled, and it is with this need in view that it has been decided to add to the department a division of medical research.

In the past, research has been undertaken by isolated individuals, in addition to their normal duties. Studies in progress at present include an investigation into kuru, an obscure nervous condition that is almost 100% fatal and probably of hereditary origin. Infant and child mortality is also of great local concern.

1. The Council's office is at 50, Merrion Square, Dublin.

MEDICAL CERTIFICATES FOR LONG ILLNESSES

THE Ministry of Pensions and National Insurance wishes to remind doctors that the Medical Certification Rules allow them, where a patient has been unfit for work for at least 6 months and incapacity is likely to last for some time to come, to give him a single certificate to cover up to 13 weeks ahead even though it may be necessary to see him more often.

This arrangement was originally made so as to reduce the amount of routine certification by doctors, and the number of times the patient has to send documents to the local offices of the Ministry. It also reduces the routine work in the local offices which has to be done on each claim for benefit. When long-term certificates are issued, local offices are able to pay sickness benefit by means of order books covering 8 or 13 weeks, instead of preparing and sending postal drafts week by week. In the last few years the number of prospective certificates issued by doctors has decreased steadily and this has added disproportionately to the work in local offices.

Local offices are writing to doctors where they know of cases in which it appears that long-term certificates might be appropriate. But it is, of course, entirely at the discretion of the doctor whether he issues long-term certificates or not, and doctors are assured that the Ministry's action is not in any way an attempt to interfere with their discretion.

University of London

Dr. R. C. Curran, senior lecturer in pathology in the University of Sheffield, has been appointed to the chair of pathology at St. Thomas's Hospital Medical School.

Dr. Curran graduated M.B. with commendation from the University of Glasgow in 1943. He served with the R.A.M.C. and held house-posts at Glasgow Royal Infirmary before he was appointed assistant pathologist and bacteriologist to Stobhill Hospital. Before taking up his present post, he was lecturer in pathology in the University of Glasgow. In 1956 he was awarded the Bellahouston medal for his M.D. thesis. His published work includes papers on collagen formation in the quartz focus, elaboration of mucopolysaccharides by vascular endothelium, and utilisation of sulphate ion by fibroblasts in quartz focus.

Dr. M. de Burgh Daly, Locke research fellow of the Royal Society in the department of physiology at University College, has been appointed to the chair of physiology at St. Bartholomew's Hospital Medical College.

Dr. de Burgh Daly studied medicine at the University of Cambridge, where he took the natural sciences tripos in 1944, and at St. Bartholomew's Hospital. After qualifying in 1947, he held a house-appointment at Barts and later became a lecturer in physiology at University College, London. In 1952 he was awarded a Rockefeller travelling fellowship and the following year the Schafer prize in physiology. He has contributed to Winton and Bayliss's *Human Physiology* and has published papers on innervation of the bronchi and on bronchomotor and pulmonary arterial reflexes.

Society of Apothecaries of London

Dr. W. S. C. Copeman has been elected master, with Dr. R. R. Trail and Dr. Charles White as wardens.

The following diplomas have been granted:

M.M.S.A.—P. R. Sathyanadhan.

L.M.S.S.A.—D. H. Perkins, J. R. Carling, M. C. Liu, I. H. Bailes, R. J. Priddy, J. R. Johnson, R. N. Brain, S. K. C. R. Villayarayan, M. A. Saber, E. M. Blenkinsopp, P. W. F. Chan, N. Mustapha, J. A. Saunders, D. F. Fergie-Woods, M. T. Haslam, H. Hunt, E. McIlwaine, P. Nour-Eldin, J. F. Rivers, M. Budd, L. B. Cannell, A. J. Casson, M. A. Gibson, A. M. Hazell, R. G. Hornung, J. G. Williams.

D.I.H.—F. de S. Donnan, G. F. Smith W. O. Thompson.

University of Otago

Next February, at the age of 70, Sir Charles Hercus will be giving up his post as dean of the Otago Medical School. He is to continue part-time work as medical secretary to the New Zealand Medical Research Council. Dr. Edward G. Sayers, C.M.G., consulting physician in Auckland, has been appointed to succeed him.

Dr. Sayers qualified in Otago, and after postgraduate study in London worked as a medical missionary in the Solomon Islands. He returned to Auckland to practise as a physician before the war, in which active service took him to various theatres, and he attained the rank of colonel. He has recently retired from the presidency of the Royal Australasian College of Physicians, and he is a fellow of the London college and an honorary fellow of the American one.

He is chairman of the New Zealand Medical Council and serves on a number of committees in the Health Department dealing with specialist services. Last year he visited Canada, the U.S.A., and Great Britain.

College of General Practitioners

Dr. E. F. Scowen will give the Pfizer lecture at 9 P.M. on Wednesday, Oct. 15, at St. Bartholomew's Hospital Medical College, London, E.C.1. His subject will be Some Difficulties in Prescribing.

British Congress of Obstetrics and Gynæcology

This congress will be held in Cardiff from July 14 to 16 under the presidency of Prof. Gilbert Strachan. The programme is to be published in November. The congress secretaries may be addressed at the Maternity Hospital, Glossop Terrace, Cardiff.

Nutrition and Teeth

The Nutrition Society will hold a symposium on this subject at the London Hospital Medical College, E.1, on Saturday, Oct. 4. Further particulars may be had from Miss D. F. Hollingsworth, c/o Ministry of Agriculture, Fisheries and Food, Great Westminster House, Horseferry Road, S.W.1.

Space Medicine

The British Interplanetary Society, with the cooperation of the Royal Air Force Institute of Aviation Medicine, is to hold a symposium on this subject at B.M.A. House, Tavistock Square, London, W.C.1, on Oct. 16 and 17. Further particulars may be had from the secretary of the society, 12, Bessborough Gardens, S.W.1.

Imperial Cancer Research Fund

The Fund has announced the following staff changes:

Dr. J. Craigie has resigned his post as director of the Fund's Mill Hill laboratories so that he can devote himself entirely to research in the laboratories. His advice on problems of research will thus continue to be available to the Fund.

Dr. R. J. C. Harris is joining the scientific staff on Oct. 1, 1958, to take up a new appointment as head of the division of experimental biology and virology. He will also be responsible (under the director, Dr. G. F. Marrian) for the general administration of the Mill Hill laboratories.

Dr. A. R. Currie, at present assistant pathologist at the Royal Infirmary, Glasgow, has been appointed head of the division of pathology, and will take up his duties on Oct. 1, 1959. The Fund is meanwhile giving financial support to the cancer research he is doing in the pathology department of the University of Glasgow.

International Federation of Medical Electronics

At a meeting held in Paris in June, at the invitation of Dr. Vladimir K. Zworykin, of the Medical Electronics Center of the Rockefeller Institute, with the cooperation of UNESCO and a number of scientific societies, 76 representatives from eleven countries unanimously agreed:

To set up an international federation of medical electronic organisations open to societies and individuals from all countries of the world; to hold an international meeting in Paris in the spring of 1959; to compile an international bibliography on medical electronics.

Interim officers elected by the group include Dr. V. K. Zworykin, president; Dr. C. N. Smyth, vice-president and chairman of publications committee; and Mr. B. Shackel, treasurer.

Royal Institute of Public Health and Hygiene

On Monday, Oct. 13, at 5 P.M., at the Institute, 28, Portland Place, London, W.1, Dr. B. G. B. Lucas will give the Bengué lecture. His subject is to be artificial aids in the control of the circulation.

Charterhouse Rheumatism Clinic

On Friday, Oct. 10, at 5.30 P.M., at 54, Weymouth Street, London, W.1, Prof. J. de Sèze, of the Centre de Rhumatologie Viggo-Petersen, Paris, will give the Gilbert Scott lecture. He is to speak on postmenopausal trophostatic pain.

Scientific Film Association

A medical section of this association is being formed and the inaugural meeting will be held on Monday, Sept. 8, at 6 P.M. at the film theatre, room 103, Shell-Mex House, Strand, London, W.C.2, when *Stress and the Adaptation Syndrome* (U.S.A. 1957) and *Jugular Venous Pulse* (Great Britain, 1958) will be shown. Further information may be had from the secretary at the association's new address, 3, Belgrave Square, London, S.W.1.

On Thursday, Oct. 2, at 3 P.M., at the Royal College of Physicians of London, Pall Mall East, S.W.1, Sir Hartley Shawcross will give the inaugural address to Charing Cross Hospital Medical School.

The National Association for the Prevention of Tuberculosis and Diseases of the Chest and Heart, with the chest clinic service of Glasgow, is holding a symposium on the catarrhal child, on Wednesday, Oct. 1, at 3.30 P.M., at the Royal Faculty of Physicians and Surgeons, 242, St. Vincent Street, Glasgow, C.2. Prof. Stanley Graham will be in the chair and the speakers will include Dr. Catriona Sinclair, Dr. A. W. Lees, Prof. J. W. Howie, Dr. William Blair, Dr. R. H. Dobbs, Prof. Wilfrid Gaisford, and Dr. R. J. Cuthbert. Tickets (10s.) may be had from the N.A.P.T. Scottish Branch, 65, Castle Street, Edinburgh, 2.

The British Commonwealth and Empire Nurses War Memorial Fund has awarded twelve scholarships for 1958–59. Nine go to nurses and midwives in the United Kingdom and three to nurses from the Commonwealth.

The Scottish group of the Nutrition Society is holding a symposium in Edinburgh on Saturday, Sept. 27, on nutritional hazards caused by radioactive contamination of foods. Further particulars may be had from Dr. J. Davidson, Rowett Research Institute, Bucksburn, Aberdeenshire.

Dr. J. W. Galloway is to succeed Dr. T. H. J. Douglas as chief dental officer of the Department of Health for Scotland at the end of the year.

Dr. J. M. Walshe is spending two months in Argentina and Chile under the auspices of the British Council. He is to visit the Universities of Buenos Aires, Cordoba, Rosario, and Chile.

The Danish Surgical Society has become a member institution of the International Federation of Surgical Colleges.

The second Doctors' Hobbies Exhibition is to be held at B.M.A. House, Tavistock Square, London, W.C.1, from Nov. 10 to 14. Entry forms may be had from the public relations officer, Benger Laboratories Ltd., Holmes Chapel, Cheshire. Entries close on Sept. 12.

The editorial and publishing offices of the *Pharmaceutical Journal* have been moved to 17, Bloomsbury Square, London, W.C.1.

A second edition of Notes on the Diagnosis of Occupational Diseases prescribed under the National Insurance (Industrial Injuries) Act has been published by H.M. Stationery Office (3s.). The notes were compiled in 1950 for the guidance of doctors examining, for the Ministry of Pensions and National Insurance, claimants to benefit. Since then three new diseases (tuberculosis; primry neoplasm of the epithelial lining of the urinary bladder, renal pelvis, or ureter; and cadmium poisoning) have been added to the schedule of prescribed diseases, and the schedule has been revised and reorganised on the lines of the recommendations made by the Industrial Injuries Advisory Council.

CORRIGENDUM: *Eponyms in Medicine.*—In this annotation (Aug. 30, p. 452) we described Thomsen's disease as amyotonia congenita, whereas it is really myotonia congenita—a much different disorder. Our error illustrates with disconcerting immediacy the need for the advice, which we offered in the same annotation, that when eponyms are used " contributors and editors must strive to ensure that they are placed in a correct context and accurately rendered ".